```
=> d his ful

     FILE 'HCAPLUS' ENTERED AT 11:07:24 ON 10 SEP 2004
                E MORIKAWA WATARU/AU
L1            22 SEA ABB=ON  ("MORIKAWA W"/AU OR "MORIKAWA WATARU"/AU)
                E MIYAMOTO SEIJI/AU
L2            65 SEA ABB=ON  "MIYAMOTO SEIJI"/AU
L3             4 SEA ABB=ON  L1 AND L2
L4            83 SEA ABB=ON  L1 OR L2
L5            11 SEA ABB=ON  L4 AND ?PLASMINOGEN?
L6             5 SEA ABB=ON  L5 AND ?METAST?

     FILE 'REGISTRY' ENTERED AT 11:22:10 ON 10 SEP 2004
L7             1 SEA ABB=ON  HEPARIN/CN
L8             2 SEA ABB=ON  LYSINE/CN
L9             1 SEA ABB=ON  PLASMIN/CN
L10            1 SEA ABB=ON  PLASMINOGEN/CN
L11            1 SEA ABB=ON  LYS-PLASMINOGEN/CN
L12            1 SEA ABB=ON  ELASTASE/CN
L13            1 SEA ABB=ON  "TRANEXAMIC ACID"/CN

     FILE 'HCAPLUS' ENTERED AT 11:24:00 ON 10 SEP 2004
L14        25224 SEA ABB=ON  L10 OR L11 OR ?PLASMINOGEN? OR LYS?(W)?PLASMINOGEN?

L15         1448 SEA ABB=ON  L14 AND ?METAST?
L16          281 SEA ABB=ON  L15 AND (?LUNG? OR ?RESPIR?)
L17           16 SEA ABB=ON  L16 AND ?KRINGLE?
L18           11 SEA ABB=ON  L16 AND (L1 OR ?HEPARIN?)
L19            9 SEA ABB=ON  L16 AND (N(W)?TERMINAL? OR ?GLYCOSYLAT?)
L20            0 SEA ABB=ON  L16 AND ?PHYSIOL?(W)?IONIC?
L21            3 SEA ABB=ON  L16 AND ?IONIC?
L22            8 SEA ABB=ON  L16 AND (?ENDOTHEL?(W)?CELLS AND ?BLOOD?(W)?VESSEL?
                )
L23            0 SEA ABB=ON  L16 AND ?INCUBAT?(6A)(L13 OR ?TRANEXAMIC?(W)?ACID)
L24            5 SEA ABB=ON  L16 AND ?INCUBAT?
L25            3 SEA ABB=ON  L16 AND (L13 OR ?TRANEXAMIC?(W)?ACID)
L26           44 SEA ABB=ON  L17 OR L18 OR L19 OR L21 OR L22 OR L24 OR L25
L27            9 SEA ABB=ON  L26 AND (?AUTOLYS? OR L12 OR ?ELASTAS? OR ?FRACTION
                ?)
L28           20 SEA ABB=ON  L26 AND (?IDENTIFY? OR ?ISOLAT? OR ?BIND? OR
                ?BOUND?)
L29            3 SEA ABB=ON  L26 AND ?CARRIER?
L30           44 SEA ABB=ON  L26 OR L27 OR L28 OR L29  44 cits from CA Plus

     FILE 'MEDLINE, BIOSIS, EMBASE, JICST-EPLUS, JAPIO' ENTERED AT 11:31:59 ON
     10 SEP 2004
L31          105 SEA ABB=ON  L30
L32           60 DUP REMOV L31 (45 DUPLICATES REMOVED)  60 cits from other d.b.'s

     FILE 'HCAPLUS' ENTERED AT 11:42:07 ON 10 SEP 2004
L33            5 SEA ABB=ON  L30 AND ?MOLECULAR?(W)(?WEIGHT? OR WT)
L34            2 SEA ABB=ON  L33 AND 38  2 cits for "mw 38 kDa" - see green tabs

     FILE 'MEDLINE, BIOSIS, EMBASE, JICST-EPLUS, JAPIO' ENTERED AT 11:44:15 ON
     10 SEP 2004
L35            7 SEA ABB=ON  L32 AND MOLECULAR?(W) WEIGHT?
L36            0 SEA ABB=ON  L35 AND 38  0 cits for "mw 38 kDa" - I looked
                at the 7 cits in L35.
```

=> d ibib abs ind l6 1-5

L6 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:750156 HCAPLUS
DOCUMENT NUMBER: 136:260855
TITLE: The accumulation of angiostatin-like fragments in human prostate carcinoma
AUTHOR(S): Migita, Toshiro; Oda, Yoshinao; Naito, Seiji; **Morikawa, Wataru**; Kuwano, Michihiko; Tsuneyoshi, Masazumi
CORPORATE SOURCE: Departments of Anatomic Pathology, Kyushu University, Fukuoka, 812-8582, Japan
SOURCE: Clinical Cancer Research (2001), 7(9), 2750-2756
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: Angiostatin, a potent inhibitor of angiogenesis and, hence, the growth of tumor cell **metastasis**, is generated by a proteolytic enzyme from **plasminogen.** However, its localization and specific enzymes have yet to be ascertained in human tissue. Exptl. Design: To elucidate the generation and the localization of angiostatin in prostate carcinoma, we examined angiostatin generation in a panel of human prostate cancer cell lines and performed immunohistochem. with the antibodies to angiostatin and prostate-specific antigen (PSA), a potent proteolytic enzyme of angiostatin in 55 cases of prostate carcinoma. Results: We demonstrated that the lysates of human prostate carcinoma cell lines could generate angiostatin-like fragments from purified human **plasminogen** but could not generate angiostatin in the absence of exogenous **plasminogen.** The fragmented proteins were reacted with the monoclonal antibody specific for **plasminogen** lysine-binding site 1 (LBS-1). Immunohistochem., the intracytoplasmic immunostaining of LBS-1 was pos. in 87.3% (48 of 55) of prostate carcinoma cases, and the immunostaining of **miniplasminogen** was neg. in all cases. There was a significant relationship between the pos. immunostaining of LBS-1 and Gleason score (P = 0.0007). The intracytoplasmic immunostaining of PSA was pos. in 37.0% (20 of 54) of prostate carcinoma cases, but there was no significant relationship between the expression of PSA and Gleason score, or between the pos. immunostaining of LBS-1 and PSA. Conclusions: These findings suggest that angiostatin is generated by prostate carcinoma cells and is accumulated within the cytoplasm. In addition, the generation of angiostatin-like fragments was correlated with tumor grade; however, PSA may not be the only enzyme for angiostatin generation in human prostate carcinoma.

CC 14-1 (Mammalian Pathological Biochemistry)
ST angiostatin **plasminogen** cytoplasm prostate carcinoma
IT Cytoplasm
Human
(accumulation of angiostatin-like fragments in human prostate carcinoma)
IT Prostate-specific antigen
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(accumulation of angiostatin-like fragments in human prostate carcinoma in relation to)
IT Prostate gland, neoplasm
(carcinoma; accumulation of angiostatin-like fragments in human prostate carcinoma)
IT Protein motifs
(**plasminogen** lysine-binding site 1; angiostatin generation from human **plasminogen** by prostate carcinoma cells)

IT 86090-08-6, Angiostatin
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(accumulation of angiostatin-like fragments in human prostate carcinoma)
IT 9001-91-6, **Plasminogen**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(angiostatin generation from human **plasminogen** by prostate carcinoma cells)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:878603 HCAPLUS
DOCUMENT NUMBER: 134:145519
TITLE: Angiostatin generation by cathepsin D secreted by human prostate carcinoma cells
AUTHOR(S): **Morikawa, Wataru**; Yamamoto, Kenji; Ishikawa, Sara; Takemoto, Sumiyo; Ono, Mayumi; Fukushi, Jun-Ichi; Naito, Seiji; Nozaki, Chikateru; Iwanaga, Sadaaki; Kuwano, Michihiko
CORPORATE SOURCE: Kikuchi Research Center, Chemo-Sero-Therapeutic Research Institute, Kumamoto, 869-1298, Japan
SOURCE: Journal of Biological Chemistry (2000), 275(49), 38912-38920
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiostatin, a potent endogenous inhibitor of angiogenesis, is generated by cancer-mediated proteolysis of **plasminogen.** The culture medium of human prostate carcinoma cells, when incubated with **plasminogen** at a variety of pH values, generated angiostatic peptides and **miniplasminogen.** The enzyme(s) responsible for this reaction was purified and identified as procathepsin D. The purified procathepsin D, as well as cathepsin D, generated two angiostatic peptides having the same NH2-terminal amino acid sequences and comprising kringles 1-4 of **plasminogen** in the pH range of 3.0-6.8, most strongly at pH 4.0 in vitro. This reaction required the concomitant conversion of procathepsin D to catalytically active pseudocathepsin D. The conversion of pseudocathepsin D to the mature cathepsin D was not observed by the prolonged incubation. The affinity-purified angiostatic peptides inhibited angiogenesis both in vitro and in vivo. Importantly, procathepsin D secreted by human breast carcinoma cells showed a significantly lower angiostatin-generating activity than that by human prostate carcinoma cells. Since deglycosylated procathepsin D from both prostate and breast carcinoma cells exhibited a similar low angiostatin-generating activity, this discrepancy appeared to be attributed to the difference in carbohydrate structures of procathepsin D mols. between the two cell types. The seminal vesicle fluid from patients with prostate carcinoma contained the mature cathepsin D and procathepsin D, but not pseudocathepsin D, suggesting that pseudocathepsin D is not a normal intermediate of procathepsin D processing in vivo. The present study provides evidence for the first time that cathepsin D secreted by human prostate carcinoma cells is responsible for angiostatin generation, thereby causing the prevention of tumor growth and angiogenesis-dependent growth of **metastases.**
CC 14-1 (Mammalian Pathological Biochemistry)
ST angiostatin cathepsin D prostate carcinoma angiogenesis

IT Angiogenesis
(angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT Prostate gland
(carcinoma; angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT Mammary gland
(carcinoma; procathepsin D secreted by human breast carcinoma cells has lower angiostatin-generating activity than that by human prostate carcinoma cells)
IT Blood vessel
(endothelium, proliferation; angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT Seminal vesicle
(fluid; angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT Cell proliferation
(vascular endothelium; angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT 9001-75-6, Pepsin 9001-91-6, **Plasminogen** 9025-26-7, Cathepsin D 86921-29-1, Procathepsin D 106096-93-9, Basic FGF 110910-42-4, Cathepsin E 323574-32-9, Pseudocathepsin D
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT 12408-02-5, Hydrogen ion, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT 86090-08-6, Angiostatin
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
IT 9001-90-5, Plasmin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(angiostatin generation by cathepsin D secreted by human prostate carcinoma cells)
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:241459 HCAPLUS
DOCUMENT NUMBER: 132:275964
TITLE: Novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments
INVENTOR(S): **Morikawa, Wataru**; Kaminaka, Kazuyoshi; Takemoto, Sumiyo; Maeda, Hiroaki; Nozaki, Chikateru; **Miyamoto, Seiji**
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020570	A1	20000413	WO 1999-JP5322	19990929
W: US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2000106882	A2	20000418	JP 1998-296095	19981002
EP 1118660	A1	20010725	EP 1999-970118	19990929
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: JP 1998-296095 A 19981002
WO 1999-JP5322 W 19990929

AB A novel aspartase, PACE4 (**plasminogen** angiostatin converting enzyme of pH 4), is prepared from cell line PC-3 that was established from human prostate cancer and characterized. PACE4 exhibits a mol. weight of 45 kDa as determined by non-reducing SDS-PAGE and LVRIPLHKFT at the N-terminus. PACE4 aspartase is highly homol. to human cathepsin D precursor and can degrade plasma proteins such as **plasminogen**, fibronectin, vitronectin, and human hepatic growth factor into fragments that have the angiostatin-like activities and thus the anti-**metastasis** effects. A pharmaceutical composition containing PACE4 for the prevention of treatment of solid cancers, diabetic retinopathy, or rheumatism is also claimed.

IC ICM C12N015-00
ICS C12N009-50; C07K014-78; C07K014-745; C07K001-22; A61K038-48

CC 7-2 (Enzymes)
Section cross-reference(s): 1, 13

ST human aspartase **metastasis** inhibitor; **plasminogen** angiostatin converting enzyme pH 4

IT Enzymes, biological studies
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(PACE4 (**plasminogen** angiostatin converting enzyme of pH 4); novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)

IT Animal cell line
(PC-3, PACE4 preparation from; novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)

IT Angiogenic factors
Angiogenic factors
Growth inhibitors, animal
Growth inhibitors, animal
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(angiogenic growth-inhibiting factors; novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)

IT Fibronectins
Hepatocyte growth factor
Vitronectin
RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(degradation by PACE4 of; novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma

protein fragments)
IT Eye, disease
(diabetic retinopathy, drug for; novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)
IT Antitumor agents
(**metastasis**; novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)
IT Antirheumatic agents
(novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)
IT 254754-41-1
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(N-terminus of human aspartase PACE4 (**plasminogen** angiostatin converting enzyme of pH 4); novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)
IT 9001-91-6, **Plasminogen**
RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(degradation by PACE4 of; novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)
IT 9027-30-9P, Aspartase
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(novel human aspartase homologous to cathepsin D precursor and use for producing anti-**metastasis** plasma protein fragments)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:239304 HCAPLUS
DOCUMENT NUMBER: 128:294008
TITLE: Fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing the same
INVENTOR(S): **Morikawa, Wataru; Miyamoto, Seiji**
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan; Morikawa, Wataru; Miyamoto, Seiji
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815643	A1	19980416	WO 1997-JP3635	19971009
W: AU, CA, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 10114796	A2	19980506	JP 1996-287651	19961009
AU 9745714	A1	19980505	AU 1997-45714	19971009
US 2002031518	A1	20020314	US 2001-989388	20011121
PRIORITY APPLN. INFO.:			JP 1996-287651 A	19961009

WO 1997-JP3635 W 19971009
US 1999-269720 A1 19990406

AB Fragments of a **plasminogen** effective in inhibiting tumor **metastasis** and growth, an enzymic process for preparing the fragments, and a tumor **metastasis** and growth inhibitor containing the fragments as the active ingredient are presented. The fragments are obtained from the elastase-induced hydrolysis product of Lys-**plasminogen** that is obtained by treating a **plasminogen** with plasmin and that preferably has a potent heparin-binding activity. Alternatively, the Lys-**plasminogen** is prepared by autolysis of **plasminogen** in the presence of tranexamic acid. The inhibitor is useful for clin. therapy of solid cancers typified by lung and colon cancers.

IC ICM C12P021-00
ICS A61K038-01

CC 16-2 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 1, 63

ST **plasminogen** fragment antitumor agent esterase; Lys **plasminogen** fragment esterase prepn antitumor; heparin binding Lys **plasminogen** fragment antitumor

IT Intestine, neoplasm
(colon; fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing same)

IT Antitumor agents
Lung, neoplasm
(fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing same)

IT 9005-49-6, Heparin, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Lys-**plasminogen** fragments binding to; fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing same)

IT 9001-91-6, Lys-**plasminogen**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(de-(1-76) derivs.; fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing same)

IT 1197-18-8, Tranexamic acid
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing same)

IT 9001-90-5, Plasmin 9013-79-0, Esterase
RL: CAT (Catalyst use); USES (Uses)
(fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing same)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:580744 HCAPLUS
DOCUMENT NUMBER: 127:173491
TITLE: Immunoassay of **plasminogen** degradation product for diagnosis of tumor
INVENTOR(S): **Morikawa, Wataru; Miyamoto, Seiji**
PATENT ASSIGNEE(S): Chemo-sero-therapeutic Research Institute, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09178744	A2	19970711	JP 1996-301364	19961025
PRIORITY APPLN. INFO.:			JP 1995-303600	19951027

AB The disclosed immunoassay uses monoclonal antibody specific for lysine-binding sites of **plasminogen** degradation product-a tumor marker. The anal. method also includes elastase digestion and affinity separation of **plasminogen** lysine-binding site I and II from intact **plasminogen** using affinity chromatog. column containing anti-**plasminogen** or affinity gel containing anti-**plasminogen** lysine-binding site antibodies. **Plasminogen** degradation products are tumor **metastasis** inhibitor via angiogenesis inhibition.

IC ICM G01N033-53
ICS G01N033-53; A61K038-48; G01N033-48; A61K039-395

CC 9-10 (Biochemical Methods)
Section cross-reference(s): 14, 15

ST **plasminogen** lysine binding site antibody tumor; affinity column elastase digestion immunoassay

IT Angiogenic factors
Angiogenic factors
Growth inhibitors, animal
Growth inhibitors, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiogenic growth-inhibiting factors; immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

IT Neoplasm
(diagnosis; immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

IT Affinity chromatography
Blood analysis
(immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

IT Antibodies
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

IT Antitumor agents
(**metastasis**; immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

IT Antibodies
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(monoclonal; immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

IT 9001-91-6P, **Plasminogen**
RL: ANT (Analyte); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(degradation products; immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

IT 9004-06-2, Elastase
RL: ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(digestion; immunoassay of **plasminogen** lysine-binding sites for diagnosis of tumor)

```
=> d que stat l30
L1            22 SEA FILE=HCAPLUS ABB=ON  ("MORIKAWA W"/AU OR "MORIKAWA
                 WATARU"/AU)
L10            1 SEA FILE=REGISTRY ABB=ON  PLASMINOGEN/CN
L11            1 SEA FILE=REGISTRY ABB=ON  LYS-PLASMINOGEN/CN
L12            1 SEA FILE=REGISTRY ABB=ON  ELASTASE/CN
L13            1 SEA FILE=REGISTRY ABB=ON  "TRANEXAMIC ACID"/CN
L14        25224 SEA FILE=HCAPLUS ABB=ON  L10 OR L11 OR ?PLASMINOGEN? OR
                 LYS?(W)?PLASMINOGEN?
L15         1448 SEA FILE=HCAPLUS ABB=ON  L14 AND ?METAST?
L16          281 SEA FILE=HCAPLUS ABB=ON  L15 AND (?LUNG? OR ?RESPIR?)
L17           16 SEA FILE=HCAPLUS ABB=ON  L16 AND ?KRINGLE?
L18           11 SEA FILE=HCAPLUS ABB=ON  L16 AND (L1 OR ?HEPARIN?)
L19            9 SEA FILE=HCAPLUS ABB=ON  L16 AND (N(W)?TERMINAL? OR ?GLYCOSYLAT
                 ?)
L21            3 SEA FILE=HCAPLUS ABB=ON  L16 AND ?IONIC?
L22            8 SEA FILE=HCAPLUS ABB=ON  L16 AND (?ENDOTHEL?(W)?CELLS AND
                 ?BLOOD?(W)?VESSEL?)
L24            5 SEA FILE=HCAPLUS ABB=ON  L16 AND ?INCUBAT?
L25            3 SEA FILE=HCAPLUS ABB=ON  L16 AND (L13 OR ?TRANEXAMIC?(W)?ACID)

L26           44 SEA FILE=HCAPLUS ABB=ON  L17 OR L18 OR L19 OR L21 OR L22 OR
                 L24 OR L25
L27            9 SEA FILE=HCAPLUS ABB=ON  L26 AND (?AUTOLYS? OR L12 OR ?ELASTAS?
                  OR ?FRACTION?)
L28           20 SEA FILE=HCAPLUS ABB=ON  L26 AND (?IDENTIFY? OR ?ISOLAT? OR
                 ?BIND? OR ?BOUND?)
L29            3 SEA FILE=HCAPLUS ABB=ON  L26 AND ?CARRIER?
L30           44 SEA FILE=HCAPLUS ABB=ON  L26 OR L27 OR L28 OR L29

=> d ibib abs l30 1-44

L30  ANSWER 1 OF 44  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:355085  HCAPLUS
DOCUMENT NUMBER:          140:369944
TITLE:                    Human tissue-specific housekeeping genes identified by
                          expression profiling
INVENTOR(S):              Aburatani, Hiroyuki; Yamamoto, Shogo
PATENT ASSIGNEE(S):       NGK Insulators, Ltd., Japan
SOURCE:                   PCT Int. Appl., 372 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2004035785         A1    20040429    WO 2002-JP10753         20021016
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
             UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       WO 2002-JP10753         20021016
```

AB Housekeeping genes commonly expressed in 35 different human tissues, oligonucleotide probes and DNA microarrays containing them, are disclosed.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:219931 HCAPLUS
DOCUMENT NUMBER: 140:248186
TITLE: Use of patterns of gene expression to **identify** tissue types and in disease diagnosis and prognosis
INVENTOR(S): Glinskii, Guennadi V.
PATENT ASSIGNEE(S): Sidney Kimmel Cancer Center, USA
SOURCE: U.S. Pat. Appl. Publ., 209 pp., which which which which
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004053317	A1	20040318	US 2003-660434	20030910
WO 2004025258	A2	20040325	WO 2003-US28707	20030910

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2002-410018P	P	20020910
US 2002-411155P	P	20020916
US 2002-429168P	P	20021125
US 2003-444348P	P	20030131
US 2003-460826P	P	20030403

AB Methods of using quant. anal. of array hybridizations to **identify** normal and diseased tissue in the diagnosis and prognosis of disease are described. The methods segregate individual samples into distinct classes using quant. measurements of expression values for selected sets of genes in individual samples compared to a reference standard Samples displaying pos. and neg. correlations of the gene expression values with the reference standard samples exhibit distinct behaviors and pathohistol. features. Also disclosed are methods for **identifying** sets of genes whose expression patterns are correlated with a phenotype. Such sets are useful for characterizing cellular differentiation pathways and states and for **identifying** potential drug discovery targets. Panels for diagnosis and determination of risk of invasive and **metastatic** forms of **lung**, prostate and breast cancer are identified. Similarly, panels indicating recurrence of the cancers and poor prognostic outcomes are identified.

L30 ANSWER 3 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:777524 HCAPLUS

DOCUMENT NUMBER: 139:287961
TITLE: A short variant of integrin α6 with possible diagnostic and therapeutic uses
INVENTOR(S): Cress, Anne E.; Edge, Albert
PATENT ASSIGNEE(S): The Arizona Board of Regents on Behalf of the University of Arizona, USA; Dyax Corporation
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003079974	A2	20031002	WO 2003-US6610	20030306
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003219837	A1	20031127	US 2003-382808	20030306
PRIORITY APPLN. INFO.:			US 2002-365370P	P 20020318

AB The invention includes ligands (and methods for **identifying** the ligands) that **bind** specifically to a naturally occurring variant of a cell surface mol., such as a naturally occurring variant of an integrin. The invention includes ligands that **bind** a naturally occurring variant of an alpha6 integrin, called alpha6p. The invention also includes methods of diagnosis and/or treatment using the ligands. Preferred ligands **bind** to the naturally occurring variant of the cell surface mol. with a higher affinity than to the unmodified cell surface mol. The protein was identified as a low mol. weight variant of integrin α6 immunopptd. from DU145H cells. The light chain of the integrin was identical to that of full-length integrin α6. This variant **bound** specifically with integrins β1 and β4 and was found in epithelial cancer cell lines and differentiating keratinocytes and had a longer half-life on the cell surface than the full-length α6.

L30 ANSWER 4 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:668100 HCAPLUS
DOCUMENT NUMBER: 140:138837
TITLE: Coelectrotransfer to skeletal muscle of three plasmids coding for antiangiogenic factors and regulatory factors of the tetracycline-inducible system: tightly regulated expression, inhibition of transplanted tumor growth, and **antimetastatic** effect
AUTHOR(S): Martel-Renoir, Dominique; Trochon-Joseph, Veronique; Galaup, Ariane; Bouquet, Celine; Griscelli, Franck; Opolon, Paule; Opolon, David; Connault, Elisabeth; Mir, Lluis; Perricaudet, Michel
CORPORATE SOURCE: Institut Gustave Roussy, UMR 8121, Vectorologie et Transfert de Genes, Villejuif, 94805, Fr.
SOURCE: Molecular Therapy (2003), 8(3), 425-433

CODEN: MTOHCK; ISSN: 1525-0016
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We describe an approach employing i.m. plasmid electrotransfer to deliver secretable forms of K1-5 and K1-3-HSA (a fusion of K1-3 with human serum albumin), which span, resp., five and three of the five **kringle** domains of **plasminogen.** A tetracycline-inducible system (Tet-On) composed of three plasmids coding, resp., for the transgene, the tetracycline transcriptional activator rtTA, and the silencer tTS was employed. K1-3-HSA and K1-5, produced from C2C12 muscle cells, were found to inhibit endothelial cell (HMEC-1) proliferation by 30 and 51%, resp. In vivo, the expression of the transgene upon doxycycline stimulation was rapid, stable, and tightly regulated (no background expression) and could be maintained for at least 3 mo. Blood half-lives of 2.1 and 3.7 days were found for K1-5 and K1-3-HSA, resp. The K1-5 protein was secreted from muscle into blood at a level of 45 ng/mL, which was sufficient to inhibit MDA-MB-231 tumor growth by 81% in nude mice and B16-F10 melanoma cell **lung** invasion in C57BL/6 mice by 73%. PECAM-1 immunostaining studies revealed modest tumor vasculature in mice expressing K1-5. In contrast, K1-3-HSA, although secreted into blood at much higher level (250 ng/mL) than K1-5, had no effect on tumor growth.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 5 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:347668 HCAPLUS
DOCUMENT NUMBER: 139:332531
TITLE: Combined treatment with verapamil, a calcium channel blocker, and B428, a synthetic uPA inhibitor, impairs the **metastatic** ability of a murine mammary carcinoma
AUTHOR(S): Todaro, Laura B.; Ladeda, Virginia; De Kier Joffe, Elisa Bal; Farias, Eduardo F.
CORPORATE SOURCE: Research Area, Institute of Oncology 'Angel H. Roffo', University of Buenos Aires, Buenos Aires, Argent.
SOURCE: Oncology Reports (2003), 10(3), 725-732
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Urokinase **plasminogen** activator (uPA) and metalloproteinases (MMP) play key roles in invasion and **metastasis**, degrading extracellular matrix compds. and modulating tumor cell motility. Their regulation is an attractive therapeutic target for controlling tumor **metastasis.** Previously we have demonstrated that urokinase overexpression in murine mammary tumor cells is regulated by a Ca2+-dependent pathway and that blockage of Ca2+ channels by verapamil partially inhibited their invasive and **metastatic** ability. Moreover, the catalytic inhibition of uPA by a synthetic uPA inhibitor B428 reduced local tumor invasiveness but not tumor cell dissemination. We evaluated the effect of a combined treatment with verapamil and B428 on the murine mammary carcinoma F3II behavior in vivo and in vitro. In vivo administration of the combined treatment was not associated to an overt toxicity. Only the daily combined treatment, beginning after tumor take, reduced the incidence and the number of spontaneous **lung** **metastasis**, while no differences were found in the s.c. growth of the primary tumor. Interestingly, a remarkable reduction in plasma MMP-9 activity was found associated to **metastasis** impairment. In addition, the number of exptl. **lung** **metastases** was also

significantly diminished, with respect to the control group, only when both compds. were co-administered daily, beginning three days after i.v. tumor cell injection. In vitro, both compds., either sep. or combined, could inhibit secreted uPA activity. F3II cell migration was significantly inhibited by **incubation** with 50 μM verapamil, 15 μM B428 or the co-treatment with 7.5 μM B428+25 μM verapamil. The cell spread was also significantly reduced when F3II cells were exposed to the compds., with an additive effect when B428 + verapamil combination was used. The combination of two compds. acting through different mol. targets may be useful to improve the control of **metastatic** dissemination.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 6 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:261008 HCAPLUS
DOCUMENT NUMBER: 138:281097
TITLE: Angiostatin fragments and method of use
INVENTOR(S): Folkman, M. Judah; O'Reilly, Michael S.; Cao, Yihai; Sim, Kim Lee
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 96 pp., Cont.-in-part of U.S. Ser. No. 335,325.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003064926	A1	20030403	US 2002-127066	20020422
US 5639725	A	19970617	US 1994-248629	19940426
US 5792845	A	19980811	US 1994-326785	19941020
US 5885795	A	19990323	US 1995-429743	19950426
US 5837682	A	19981117	US 1996-612788	19960308
US 5945403	A	19990831	US 1997-866735	19970530
US 6024688	A	20000215	US 1998-66028	19980424
US 2002164717	A1	20021107	US 1999-335325	19990617
US 6521439	B2	20030218		
US 2002037847	A1	20020328	US 2001-761120	20010116
US 2001029246	A1	20011011	US 2001-788142	20010216
US 2004002459	A1	20040101	US 2003-402364	20030328

PRIORITY APPLN. INFO.:

US 1994-248629	A2	19940426
US 1994-326785	A2	19941020
US 1995-429743	A2	19950426
US 1996-612788	A3	19960308
US 1997-866735	A3	19970530
US 1998-66028	A3	19980424
US 1999-309821	B1	19990511
US 1999-335325	A1	19990617
US 1999-338387	B1	19990622
US 2001-788142	A2	20010216
US 2001-761120	B1	20010116

AB Fragments of an endothelial cell proliferation inhibitor and method of use therefor are provided. The endothelial proliferation inhibitor is a protein derived from **plasminogen**, or more specifically is an angiostatin fragment. The angiostatin fragments generally correspond to **kringle** structures occurring within the endothelial cell proliferation inhibitor. The endothelial cell inhibiting activity of

these fragments provides a means for inhibiting angiogenesis of tumors and for treating angiogenic-mediated disease. Angiostatin was cloned in Pichia pastoris and purified from fermentation broth by lysine-Sepharose 4B. The purified recombinant angiostatin inhibited the bFGF-driven proliferation of bovine **endothelial cells** in vitro in a dose dependent manner and suppressed **metastases** of Lewis **lung** carcinoma in mice.

L30 ANSWER 7 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:937303 HCAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2002355079	A2	20021210	JP 2002-69354		20020313
PRIORITY APPLN. INFO.:			JP 2001-73183	A	20010314
			JP 2001-74993	A	20010315
			JP 2001-102519	A	20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L30 ANSWER 8 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:845509 HCAPLUS
DOCUMENT NUMBER: 137:347524
TITLE: Inhibition of angiogenesis by delivery of nucleic acids encoding anti-angiogenic polypeptides derived from **plasminogen**
INVENTOR(S): Papkoff, Jackie
PATENT ASSIGNEE(S): Valentis, Inc., USA; Pfizer, Inc.
SOURCE: U.S., 46 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 6475784	B1	20021105	US 1998-192012	19981113
PRIORITY APPLN. INFO.:			US 1997-66020P P	19971114

AB This invention pertains to the field of inhibition of angiogenesis in mammals by delivery of angiogenesis inhibitors derived from **plasminogen.** The angiogenesis inhibitors are delivered in polypeptide or nucleic acid form. The anti-angiogenic polypeptides include at least **kringles** 1-3 of **plasminogen,** extending from about amino acid 97 to at least amino acid 462 of **plasminogen.** The sequence encoding the anti-angiogenic polypeptide generally is operably linked to a polynucleotide sequence encoding a signal peptide. The invention also provides methods of using the polypeptides and nucleic acids for inhibiting angiogenesis and other conditions characterized by undesirable endothelial cell proliferation. The invention also provides **endothelial cells** and tumor cells that contain a recombinant expression cassette which includes a polynucleotide sequence encoding a signal peptide operably linked to a polynucleotide sequence encoding an anti-angiogenic polypeptide. A plasmid vector, pMB249, was constructed which encodes mouse mouse **kringle** domains of **plasminogen** linked to IgK signal peptide. Inhibition of human **lung** endothelial cell proliferation by transfection with pMB249 was demonstrated. A decrease in the number and size of **lung metastases** in the mouse Lewis **lung** model was also demonstrated.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 9 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:722324 HCAPLUS
DOCUMENT NUMBER: 139:30250
TITLE: Lovastatin alters cytoskeleton organization and inhibits experimental **metastasis** of mammary carcinoma cells
AUTHOR(S): Farina, Hernan G.; Bublik, Debora R.; Alonso, Daniel F.; Gomez, Daniel E.
CORPORATE SOURCE: Laboratory of Molecular Oncology, Quilmes National University, Buenos Aires, Argent.
SOURCE: Clinical & Experimental Metastasis (2002), 19(6), 551-560
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lovastatin is a competitive inhibitor of 3-hydroxy 3-methylglutaryl CoA reductase, the key regulatory enzyme of cholesterol biosynthesis. This enzyme catalyzes the formation of mevalonate, which is also the precursor of isoprenoid moieties, such as farnesol and geraniol, that are incorporated into several mols. essential for tumor cell signaling. Here, we describe that pretreatment with a non-cytotoxic concentration of lovastatin (10 μM) dramatically inhibited the **metastatic** ability of F3II mammary carcinoma cells in syngeneic BALB/c mice. Similarly, daily i.p. treatment of animals with a well-tolerated dose of lovastatin (10 mg/kg/day) significantly reduced the number of exptl. **lung metastases.** In vitro, **incubation** of F3II monolayers in the presence of lovastatin caused a rounded-cell morphol. Immunofluorescence anal. revealed a lack of cortical actin organization, micrutubule disruption and inhibition of integrin-mediated focal contacts in lovastatin-treated cells. Exposure of F3II cells to lovastatin significantly inhibited tumor cell adhesion and migration, and **coincubation** with the cholesterol precursor mevalonate prevented

these effects. Lovastatin reduced membrane localization of Rho protein, a signaling mol. involved in the regulation of actin-based cell motility that needs geranylation for membrane association and activation. In addition, lovastatin induced a dose-dependent inhibition in the secretion of urokinase, a key proteolytic enzyme during tumor invasion and **metastasis**, and a significant increase of tissue-type **plasminogen** activator, a marker of good prognosis in mammary cancer. These data suggest that **antimetastatic** properties of lovastatin are strongly associated with alterations in cytoskeleton organization and the consequent modulation of adhesion, motility and proteolysis.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 10 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:429035 HCAPLUS
DOCUMENT NUMBER: 137:15769
TITLE: Anti-angiogenic polypeptides use for cancer therapy
INVENTOR(S): Waisman, David M.; Kassam, Geetha; Kwon, Mijung
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044328	A2	20020606	WO 2001-US44515	20011128
WO 2002044328	A3	20030403		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002039366	A5	20020611	AU 2002-39366	20011128
EP 1337548	A2	20030827	EP 2001-987119	20011128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004082030	A1	20040429	US 2003-415012	20030422
PRIORITY APPLN. INFO.:			US 2000-253725P P	20001128
			WO 2001-US44515 W	20011128

AB This invention relates to angiogenesis and anti-angiogenic polypeptides which are related to **plasminogen** and their use for inhibiting angiogenesis. Anti-angiogenic polypeptides disclosed are A61 or p22. Also disclosed are methods of making the polypeptides and methods of treating subjects having angiogenic diseases or conditions.

L30 ANSWER 11 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:935357 HCAPLUS
DOCUMENT NUMBER: 136:64120
TITLE: Sequences of human urokinase-type **plasminogen** activators(uPA) and uses for modulating muscle cell and tissue contractility
INVENTOR(S): Cines, Douglas B.; Higazi, Abd Al-Roof

PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097752	A2	20011227	WO 2001-US18976	20010613
WO 2001097752	A3	20020627		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001069803	A5	20020102	AU 2001-69803	20010613
US 2002131964	A1	20020919	US 2001-880503	20010613
PRIORITY APPLN. INFO.:			US 2000-212874P P	20000620
			WO 2001-US18976 W	20010613

AB The present invention relates to compns. and methods comprising one or more domains of urokinase-type **plasminogen** activator (uPA) in an amount effective to modulate one or more of the contractility and angiogenic activity of a mammalian muscle or endothelial cell or tissue for use in the treatment of a disease or condition having as a symptom thereof one or more of abnormal muscle cell or tissue contractility and abnormal angiogenic activity. The one or more domains of uPA can be present in the inventive compns. and methods either as part of the full uPA mol. in either single chain or two chain form (scuPA or tcuPA), or as an **isolated** polypeptide, or a fragment of the uPA mol. (e.g., the amino terminal fragment "ATF"), or a deletion mutant of the uPA mol. The inventive methods comprise administering to a mammal afflicted with such a disease or condition the inventive composition, and modulating one or more of the contractility and the angiogenic activity of the muscle or endothelial cell or tissue, thereby treating the disease or condition. Kits for treating such diseases are also included.

L30 ANSWER 12 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:752361 HCAPLUS
DOCUMENT NUMBER: 136:17108
TITLE: p22 Is a Novel **Plasminogen** Fragment with Antiangiogenic Activity
AUTHOR(S): Kwon, Mijung; Yoon, Chang-Soon; Fitzpatrick, Sandra; Kassam, Geetha; Graham, Kenneth S.; Young, Mary K.; Waisman, David M.
CORPORATE SOURCE: Cancer Biology Research Group Departments of Biochemistry & Molecular Biology and Oncology, University of Calgary, Calgary, AB, T2N 4N1, Can.
SOURCE: Biochemistry (2001), 40(44), 13246-13253
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tumor or tumor-associated cells cleave circulating **plasminogen** into three or four **kringle**-containing antiangiogenic fragments,

collectively referred to as angiostatin. Angiostatin blocks tumor growth and **metastasis** by preventing the growth of endothelial cells that are critical for tumor vascularization. Here, we show that cancer and normal cells convert **plasminogen** into a novel 22 kDa fragment (p22). Production of this **plasminogen** fragment in a cell-free system has allowed characterization of the structure and activity of the protein. The p22 consists of amino acid residues 78-180 of **plasminogen** and therefore embodies the first **plasminogen** **kringle** (residues 84-162) as well as addnl. N- and C-terminal residues. CD and intrinsic fluorescence spectrum anal. have defined structural differences between p22 and recombinant **plasminogen** **kringle** 1 (rK1), therefore suggesting a unique conformation for **kringle** 1 within p22. Proliferation of capillary endothelial cells but not cells of other lineages was selectively inhibited by p22 in vitro. In addition, p22 prevented vascular growth of chick chorioallantoic membranes (CAMs) in vivo. Furthermore, administration of p22 at low dose suppressed the growth of murine Lewis **lung** carcinoma (LLC) **metastatic** foci in vivo. This is the first identification of a single **kringle**-containing antiangiogenic **plasminogen** fragment produced under physiol. conditions.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 13 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:729551 HCAPLUS

DOCUMENT NUMBER: 136:395447

TITLE: Adenoviral vector expressing murine angiostatin inhibits a model of breast cancer **metastatic** growth in the **lungs** of mice

AUTHOR(S): Gyorffy, Steve; Palmer, Kay; Gauldie, Jack

CORPORATE SOURCE: Department of Pathology and Molecular Medicine, Centre for Gene Therapeutics, McMaster University, Hamilton, ON, L8N 3Z5, Can.

SOURCE: American Journal of Pathology (2001), 159(3), 1137-1147
CODEN: AJPAA4; ISSN: 0002-9440

PUBLISHER: American Society for Investigative Pathology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Angiostatin, an internal fragment of **plasminogen**, has been shown to inhibit the process of angiogenesis or neovascularization. In this study, we have expressed the cDNA for murine angiostatin under the control of the human cytomegalovirus promoter from a human type-5 adenovirus and shown that this vector produces a protein which retains biol. activity. Angiostatin expression was determined by Northern blot anal. and Western immunoblotting. Ad-angiostatin, but not a control vector Ad-d170, significantly reduced the viability of infected human umbilical cord vein **endothelial cells** (HUVEC) in vitro. In an in vivo model of basic fibroblast growth factor-induced angiogenesis, Ad-angiostatin (1 + 109 pfu) could inhibit endothelial cell migration and the formation of capillaries within a Matrigel plug which had been implanted for one week s.c. into C57BL/6 mice. **Endothelial cells** in these plugs had an altered, rounded, phenotype with dark picnotic nuclei indicative of apoptosis, which was confirmed using transmission electron microscopy. In contrast, **endothelial cells** from bFGF alone or in combination with the control vector-treated plugs retained the long spindle shape characteristic of **endothelial** **cells.** Intranasal delivery of Ad-angiostatin into the **lungs** of FVB/n mice demonstrated comparable cellular infiltration in the recovered bronchoalveolar lavage fluid with no signs of abnormal

pathol. as compared to PBS or control vector-treated animals. In a pulmonary **metastatic** breast cancer model, the delivery of Ad-angiostatin (1 + 109 pfu) to the **lung** significantly delayed tumor growth as measured by the number of visible surface tumor nodules. This study has demonstrated that the specific targeting of tumors to inhibit angiogenesis using an adenovirus expressing angiostatin, may deliver localized concns. of protein having a greater impact on inhibition of tumor growth.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 14 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:545502 HCAPLUS
DOCUMENT NUMBER: 135:117219
TITLE: Hapten-coagulation agent-antineoplastic agent combinations for treating neoplasms
INVENTOR(S): Yu, Baofa
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001052868	A1	20010726	WO 2001-US1737	20010118
WO 2001052868	C2	20030116		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002044919	A1	20020418	US 2001-765060	20010117
JP 2004505009	T2	20040219	JP 2001-552915	20010118
PRIORITY APPLN. INFO.:			US 2000-177024P P	20000119
			WO 2001-US1737 W	20010118

AB Methods are provided for treating neoplasms, tumors and cancers, using one or more haptens and coagulation agents or treatments, alone or in combination with other anti-neoplastic agents or treatments. Also provided are combinations, and kits containing the combinations for effecting the therapy.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 15 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:401282 HCAPLUS
DOCUMENT NUMBER: 136:95650
TITLE: cDNA transfection of amino-terminal fragment of urokinase efficiently inhibits cancer cell invasion and **metastasis**
AUTHOR(S): Zhu, Fuxiang; Jia, Shidong; Xing, Guichun; Gao, Linlu; Zhang, Lingqiang; He, Fuchu
CORPORATE SOURCE: Beijing Institute of Radiation Medicine, Beijing, Peop. Rep. China

SOURCE: DNA and Cell Biology (2001), 20(5), 297-305
CODEN: DCEBE8; ISSN: 1044-5498
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Focusing of urokinase-type **plasminogen** activator (uPA) to the cell surface via **binding** to its specific receptor (uPAR, CD87) is critical for tumor invasion and **metastasis**. Consequently, the inhibition of uPA-uPAR interaction on the cell surface might be a promising anti-invasion and anti-**metastasis** strategy. We examined the effects of cDNA transfection of the human uPA amino-terminal fragment (ATF) on invasion and **metastasis** of cancer cells. First, a highly **metastatic** human **lung** giant-cell carcinoma cell line (PG), used as the target cell for evaluation of this effect, was demonstrated to express both uPA and uPAR. Then, ATF, which contains an intact uPAR **binding** site but is catalytically inactive, was designed as an antagonist of uPA-uPAR interaction and was transfected into PG cells. [3H]-Thymidine incorporation and cell growth curves indicated that expressed ATF did not affect the proliferation of transfected cells. However, anal. by SEM revealed that ATF changed the host cells from the typical invasive phenotype to a noninvasive one. Correspondingly, the modified Boyden chamber test in vitro showed that ATF expression significantly decreased the invasive capacity of transfected cells. Furthermore, in the spontaneous **metastasis** model, it was confirmed in vivo that expressed ATF remarkably inhibited **lung** **metastasis** of implanted ATF-transfected PG cells. In summary, autocrine ATF could act as an antagonist of uPA-uPAR interaction, and ATF cDNA transfection could efficiently inhibit the invasion and **metastasis** of the cancer cells. Inhibition of uPA-uPAR interaction on the cell surface might be a promising anti-invasion and anti-**metastasis** strategy.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 16 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:700263 HCAPLUS
DOCUMENT NUMBER: 133:361424
TITLE: Profiling the downstream genes of tumor suppressor PTEN in **lung** cancer cells by complementary DNA microarray
AUTHOR(S): Hong, Tse-Ming; Yang, Pan-Chyr; Peck, Konan; Chen, Jeremy J. W.; Yang, Shuenn-Chen; Chen, Yen-Chu; Wu, Cheng-Wen
CORPORATE SOURCE: Institute of Biomedical Sciences, National Health Research Institute, Graduate Institute of Molecular Biology, College of Medicine, Academia Sinica, National Taiwan University, Taipei, Taiwan
SOURCE: American Journal of Respiratory Cell and Molecular Biology (2000), 23(3), 355-363
CODEN: AJRBEL; ISSN: 1044-1549
PUBLISHER: American Thoracic Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The phosphatase and tensin homol. deleted on chromosome 10 (PTEN) is a tumor suppressor gene with sequence homol. to tyrosine phosphatases and the cytoskeletal proteins tensin and auxilin. PTEN has recently been shown to inhibit cell migration and the spreading and formation of focal adhesions. This study investigated the role of PTEN in carcinoma invasion in a **lung**-cancer cell line and examined the downstream genes regulated by PTEN. We have previously established a cell-line model in

human **lung** adenocarcinoma with different invasive abilities and **metastatic** potentials. Examining PTEN gene expression in these cell lines, we found that a homozygous deletion in exon 5 is associated with high invasive ability. We then constructed stable constitutive and inducible wild-type PTEN-overexpressed transfectants in the highly invasive cell line CL1-5. We found that an overexpression of PTEN can inhibit invasion in **lung** cancer cells. To further explore the downstream genes regulated by PTEN, a high-d. cDNA microarray technique was used to profile gene changes after PTEN overexpression. Our results indicate a panel of genes that can be modulated by PTEN. PTEN overexpression downregulated genes, including integrin α6, laminin β3, **heparin-binding** epidermal growth factor-like growth factor, urokinase-type **plasminogen** activator, myb protein B, Akt2, and some expressed sequence tag (EST) clones. In contrast, PTEN overexpression upregulated protein phosphatase 2A1B, ubiquitin protease (unph), secreted phosphoprotein 1, leukocyte **elastase** inhibitor, nuclear factor-κB, cAMP response element **binding** protein, DNA ligase 1, heat shock protein 90, and some EST genes. Northern hybridization and flow cytometry anal. also confirmed that PTEN overexpression results in the reduced expression of the integrin α6 subunit. The results of this study indicate that PTEN overexpression may inhibit **lung** cancer invasion by downregulation of a panel of genes including integrin α6. The cDNA microarray technique may be an effective tool to study the downstream function of a tumor suppressor gene.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 17 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:575162 HCAPLUS
DOCUMENT NUMBER: 134:69503
TITLE: Soluble fibrin augments platelet/tumor cell adherence in vitro and in vivo, and enhances experimental **metastasis**
AUTHOR(S): Biggerstaff, J. P.; Seth, N.; Amirkhosravi, A.; Amaya, M.; Fogarty, S.; Meyer, T. V.; Siddiqui, F.; Francis, J. L.
CORPORATE SOURCE: Research and Clinical Laboratories, Walt Disney Memorial Cancer Institute at Florida Hospital, Orlando, FL, 32804, USA
SOURCE: Clinical & Experimental Metastasis (2000), Volume Date 1999, 17(8), 723-730
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There is considerable evidence for a relationship between hemostasis and malignancy. Since platelet adhesion to tumor cells has been implicated in the **metastatic** process and plasma levels of fibrinogen (Fg) and soluble fibrin (sFn) monomer are increased in cancer, the authors hypothesized that these mols. might enhance tumor-platelet interaction. The authors therefore studied **binding** of sFn monomer to tumor cells in a static microplate adhesion assay and determined the effect of pre-treating tumor cells with sFn on tumor cell-induced thrombocytopenia and exptl. **metastasis.** Soluble fibrin (produced by adding thrombin to FXIII- and **plasminogen**-free Fg in the presence of Gly-Pro-Arg-Pro-amide (GPRP-NH2)) significantly increased platelet adherence to tumor cells. This effect was primarily mediated by the integrins αIIbβ3 on the platelet and CD 54 (ICAM-1) on the tumor cells. Platelets adhered to untreated A375 cells (28

platelets/tumor cell) and this was not significantly affected by pre-treatment of the tumor cells with fibrinogen or GPRP-NH2. Although thrombin treatment increased adherence, pre-**incubation** of the tumor cells with sFn resulted in a further increase in platelet **binding** to tumor cells. In contrast to untreated tumor cells, i.v. injection of sFn-treated A 375 cells reduced the platelet count in anticoagulated mice, supporting the in vitro finding that sFn enhanced tumor cell-platelet adherence. In a more aggressive model of exptl. **metastasis**, treating tumor cells with sFn enhanced **lung** seeding by 65% compared to untreated cells. Extrapolation of these data to the clin. situation suggests that coagulation activation, and subsequent increase in circulating Fn monomer, may enhance platelet adhesion to circulating tumor cells and thereby facilitate **metastatic** spread.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 18 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:318992 HCAPLUS
DOCUMENT NUMBER: 133:218299
TITLE: A novel strategy for the tumor angiogenesis-targeted gene therapy: generation of angiostatin from endogenous **plasminogen** by protease gene transfer
AUTHOR(S): Matsuda, Kant M.; Madoiwa, Seiji; Hasumi, Yoko; Kanazawa, Takeharu; Saga, Yasushi; Kume, Akihiro; Mano, Hiroyuki; Ozawa, Keiya; Matsuda, Michio
CORPORATE SOURCE: Division of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical School, Tochigi-Ken, 329-0498, Japan
SOURCE: Cancer Gene Therapy (2000), 7(4), 589-596
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB When NIH 3T3 fibroblasts were transduced with a retroviral vector containing a cDNA for porcine pancreatic **elastase** 1 and cultured in the presence of affinity-purified human **plasminogen**, the exogenously added **plasminogen** was digested to generate the **kringle** 1-3 segment known as angiostatin, a potent angiogenesis inhibitor. This was evidenced by immunoblot anal. of the **plasminogen** digests using a monoclonal antibody specifically reacting with the **kringle** 1-3 segment, and by efficient inhibition of proliferation of human umbilical vein endothelial cells by the **plasminogen** digests **isolated** from the culture medium of 3T3 fibroblasts. However, when Lewis **lung** carcinoma cells were transduced with the same vector and injected s.c. into mice in their back or via the tail vein, their growth at the injection sites or in the **lungs** was markedly suppressed compared with the growth of similarly treated nontransduced Lewis **lung** carcinoma cells. Nevertheless, the transduced cells were able to grow as avidly as the control cells in vitro. Assuming that the **elastase** 1 secreted from the transduced cells is likely to be exempt from rapid inhibition by its physiol. inhibitor, α1-protease inhibitor, as shown in the inflammatory tissues, the **elastase** 1 secreted from the tumor cells may effectively digest the **plasminogen** that is abundantly present in the extravascular spaces and generate the **kringle** 1-3 segment in the vicinity of implanted tumor cell clusters. Although the selection of more profitable virus vectors and cells to be transduced awaits further studies, such a protease gene transfer strategy may provide us with a new approach to

anti-angiogenesis gene therapy for malignant tumors and their **metastasis** in vivo.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 19 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:304018 HCAPLUS
DOCUMENT NUMBER: 133:250551
TITLE: Effect of hyperthermia on the viability and the fibrinolytic potential of human cancer cell lines
AUTHOR(S): Fukao, H.; Ikeda, M.; Ichikawa, T.; Inufusa, H.; Okada, K.; Ueshima, S.; Matsuo, O.
CORPORATE SOURCE: Department of Physiology, Kinki University School of Medicine, Osakasayama City, Osaka, Japan
SOURCE: Clinica Chimica Acta (2000), 296(1-2), 17-33
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of heat treatment on the viability and fibrinolytic potential of four cultured human carcinoma cell lines, fibrosarcoma cells (HT-1080), **lung** adenocarcinoma cells with highly **metastatic** potential (HAL-8), melanoma cells (Bowes) and osteosarcoma cells (NY), determined by measuring their levels of urokinase-type **plasminogen** activator (u-PA) and its specific receptor (u-PAR), were investigated by comparing them with those of human umbilical vein endothelial cells (HUVECs). HUVECs **incubated** at 43° for 120 min exhibited no decrease in viability but exhibited an increase in both u-PA and u-PAR. HT-1080 and HAL-8 showed a moderately high heat-resistance (viability, 60-90%) that correlated with the reduction of u-PAR but not u-PA. On the other hand, Bowes and NY cells, with poor heat-resistance (viability, 20-50%), exhibited stronger cell-associated u-PA activity when they survived at 43° for 120 min. Since the u-PA/u-PAR system is directly involved in the invasiveness and **metastatic** potential of carcinoma cells, hyperthermia would alter the biol. activity of these carcinoma cells.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 20 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:778288 HCAPLUS
DOCUMENT NUMBER: 132:106219
TITLE: Inhibition of tumor growth correlates with the expression level of a human angiostatin transgene in transfected B16F10 melanoma cells
AUTHOR(S): Ambs, Stefan; Dennis, Steven; Fairman, Jeff; Wright, Meredith; Papkoff, Jacqueline
CORPORATE SOURCE: Valentis Inc., Burlingame, CA, 94010, USA
SOURCE: Cancer Research (1999), 59(22), 5773-5777
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although the therapeutic value of angiostatin, a proteolytic fragment of **plasminogen**, has been recognized for the treatment of cancer, the production of bioactive angiostatin remains a difficult task. Here we report that expression of a cDNA encoding a secreted, four-**kringle** human angiostatin inhibited tumor growth of B16F10 melanoma cells in mice but did not suppress tumor cell growth in culture. After transfection and selection, stable expression of the angiostatin cDNA was demonstrated in

several B16F10 clones by quant. mRNA anal. using the Taqman method. Cells that expressed angiostatin at either a low, medium, or high level were injected into C57BL/6 mice. s.c. Growth of B16F10 tumors was diminished by the angiostatin transgene, and the inhibition was directly proportional to the expression level of angiostatin in the transfected cells. However, suppression of s.c. tumor growth was transient, and eventually, tumors emerged with a strongly decreased expression of the transgene. Angiostatin expression also reduced **lung metastasis** from i.v.-injected B16F10 cells. Our data indicate that a cDNA encoding bioactive human angiostatin is potentially useful for gene therapy of human cancers, but the delivery of the transgene may require repeated dosing to achieve sustained dormancy of primary tumors and cancer **metastases.**

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 21 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:669909 HCAPLUS
DOCUMENT NUMBER: 132:18477
TITLE: The Tumor-Suppressing Activity of Angiostatin Protein Resides within **Kringles** 1 to 3
AUTHOR(S): MacDonald, Nicholas J.; Murad, Amy Chang; Fogler, William E.; Lu, Yingyu; Sim, B. K. L.
CORPORATE SOURCE: EntreMed, Inc., Rockville, MD, 20850, USA
SOURCE: Biochemical and Biophysical Research Communications (1999), 264(2), 469-477
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiostatin protein, which comprises the first four **kringle** domains of **plasminogen**, is an endogenous inhibitor of angiogenesis that inhibits the growth of exptl. primary and **metastatic** tumors. Truncation of Angiostatin K1-4 to K1-3 retained the activity of Angiostatin. We recombinantly expressed full-length human Angiostatin protein corresponding to the first four **kringle** domains of human **plasminogen** and a truncated form of the Angiostatin protein, **kringles** 1-3. Purified recombinant Angiostatin K1-3 and K1-4 proteins inhibited the formation of exptl. B16-BL6 **lung metastases** by greater than 80% when administered at 30 nmol/kg/day. We demonstrate for the first time that Angiostatin protein, consisting of the first three **kringle** domains of human **plasminogen**, has in vivo biol. activity in this assay indistinguishable from that of the full-length Angiostatin K1-4 protein and that the fourth **kringle** of **plasminogen**, when linked in sequence to K1-3, plays no direct role in the antitumor activity of Angiostatin. (c) 1999 Academic Press.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 22 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:529341 HCAPLUS
DOCUMENT NUMBER: 131:155517
TITLE: Methods and reagents for the rapid and efficient **isolation** of circulating cancer cells using immunomagnetic enrichment combined with flow cytometric and immunocytochemical analysis
INVENTOR(S): Terstappen, Leon W. M. M.; Rao, Galla Chandra; Uhr, Jonathan W.; Racila, Emilian V.; Liberti, Paul A.
PATENT ASSIGNEE(S): Immunivest, USA; University of Texas Southwestern

Medical Center
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9941613	A1	19990819	WO 1999-US3073		19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2320418	AA	19990819	CA 1999-2320418		19990212
CA 2432361	AA	19990819	CA 1999-2432361		19990212
CA 2432363	AA	19990819	CA 1999-2432363		19990212
AU 9927636	A1	19990830	AU 1999-27636		19990212
AU 760560	B2	20030515			
BR 9907852	A	20001024	BR 1999-7852		19990212
EP 1062515	A1	20001227	EP 1999-908132		19990212
R: DE, FR, GB, IT, NL					
JP 2002503814	T2	20020205	JP 2000-531745		19990212
US 2003129676	A1	20030710	US 2002-269579		20021011
PRIORITY APPLN. INFO.:			US 1998-74535P	P	19980212
			US 1998-110202P	P	19981130
			US 1998-110279P	P	19981130
			CA 1999-2320418	A3	19990212
			US 1999-248388	A3	19990212
			WO 1999-US3073	W	19990212
			US 2001-904472	A1	20010713

AB A highly sensitive assay is disclosed which combines immunomagnetic enrichment with multiparameter flow cytometric and immunocytochem. anal. to detect, enumerate and characterize carcinoma cells in the blood. The assay can detect one epithelial cell or less in 1 mL of blood and has a greater sensitivity than conventional PCR or immunohistochem. by 1-2 orders of magnitude. In addition, the assay facilitates the biol. characterization and staging of carcinoma cells. Levels of circulating epithelial cells were determined in peripheral blood samples from breast, prostate, and colon cancer patients and in normal controls. Blood was treated with anti-epithelial cell adhesion mol. (EpCAM) monoclonal antibodies coupled to magnetic nanoparticles and magnetically separated The collected **fraction** was treated with FACS permeabilization solution, magnetically separated, and treated with phycoerythrin conjugated anti-cytokeratin monoclonal antibody and peridinin chlorophyll protein-labeled CD45. Magnetically separated material was further treated with a nucleic acid dye. The samples were analyzed by FACS flow cytometry.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 23 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:205255 HCAPLUS
DOCUMENT NUMBER: 130:232478

TITLE: Manufacture of angiostatin for use in prevention of vascularization of tumors
INVENTOR(S): O'Reilly, Michael S.; Folkman, M. Judah; Sim, Kim Lee
PATENT ASSIGNEE(S): The Children's Medical Center Corporation, USA
SOURCE: U.S., 55 pp., Cont.-in-part of U.S. Ser. No. 326,785.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5885795	A	19990323	US 1995-429743	19950426
US 5639725	A	19970617	US 1994-248629	19940426
US 5792845	A	19980811	US 1994-326785	19941020
CA 2219081	AA	19961114	CA 1996-2219081	19960426
WO 9635774	A2	19961114	WO 1996-US5856	19960426
WO 9635774	A3	19970213		
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
AU 9655795	A1	19961129	AU 1996-55795	19960426
AU 709633	B2	19990902		
EP 824546	A2	19980225	EP 1996-913208	19960426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1195375	A	19981007	CN 1996-194077	19960426
JP 11508228	T2	19990721	JP 1996-534104	19960426
BR 9608326	A	20000308	BR 1996-8326	19960426
NZ 332903	A	20000428	NZ 1996-332903	19960426
JP 2001151691	A2	20010605	JP 2000-308481	19960426
NZ 307044	A	20020301	NZ 1996-307044	19960426
NO 9704943	A	19971218	NO 1997-4943	19971024
US 2003064926	A1	20030403	US 2002-127066	20020422
US 2004023877	A1	20040205	US 2003-401108	20030327

PRIORITY APPLN. INFO.:

US 1994-248629	A2	19940426
US 1994-326785	A2	19941020
US 1995-429743	A	19950426
US 1996-605598	A	19960222
US 1996-612788	A	19960308
JP 1996-534104	A3	19960426
NZ 1996-307044	A1	19960426
WO 1996-US5856	W	19960426
US 1997-866735	A3	19970530
US 1997-989477	B2	19971212
US 1998-66028	A3	19980424
US 1999-309821	B1	19990511
US 1999-335325	A1	19990617
US 1999-338387	B1	19990622
US 2001-788142	A2	20010216

AB Methods of manufacturing the angiogenesis inhibitor angiostatin for use in the treatment of tumors by inhibition of neovascularization are described. Angiostatin is **isolated** from the blood or urine as a single peak from C4-reverse phase high performance liquid chromatog. It may be manufactured by expression of the cloned gene in a microbial host such as Escherichia

coli. Expts. demonstrating the effectiveness of angiostatin in inhibiting the vascularization of a number of **metastatic** tumor cell lines is demonstrated. Angiostatin manufactured in Escherichia coli and a cDNA for angiostatin were also effective in inhibition of tumor growth in mice.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 24 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:811977 HCAPLUS
DOCUMENT NUMBER: 130:180798
TITLE: Matrix metalloproteinases generate angiostatin: effects on neovascularization
AUTHOR(S): Cornelius, Lynn A.; Nehring, Lesllie C.; Harding, Elizabeth; Bolanowski, Mark; Welgus, Howard G.; Kobayashi, Dale K.; Pierce, Richard A.; Shapiro, Steven D.
CORPORATE SOURCE: Div. Dermatol., Dep. Med., Washington Univ. Sch. Med., St. Louis, MO, 63141, USA
SOURCE: Journal of Immunology (1998), 161(12), 6845-6852
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiostatin, a cleavage product of **plasminogen**, has been shown to inhibit endothelial cell proliferation and **metastatic** tumor cell growth. Recently, the production of angiostatin has been correlated with tumor-associated macrophage production of elastolytic metalloproteinases in a murine model of Lewis **lung** call carcinoma. In this report the authors demonstrate that purified murine and human matrix metalloproteinases generate biol. functional angiostatin from **plasminogen**, macrophage **elastase** (MMP-12 or MME) proved to be the most efficient angiostatin-producing MMP. MME was followed by gelatinases and then the stomelysins in catalytic efficiency; interstitial collagenases had little capacity to generate angiostatin. Both recombinant angiostatin and angiostatin generated from recombinant MME-treated **plasminogen** inhibited human microvascular endothelial cell proliferation and differentiation in vitro. Finally, employing macrophages **isolated** from MME-deficient mice and their wild-type littermates, the authors demonstrate that MME is required for the generation of angiostatin that inhibits the proliferation of human microvascular **endothelial cells.**
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 25 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:795048 HCAPLUS
DOCUMENT NUMBER: 130:47467
TITLE: Angiostatin fragments for inhibiting angiogenesis of tumors and treatment of angiogenesis-mediated diseases
INVENTOR(S): Folkman, M. Judah; O'Reilly, Michael S.
PATENT ASSIGNEE(S): The Children's Medical Center Corporation, USA
SOURCE: PCT Int. Appl., 165 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9854217		A1	19981203	WO 1998-US10979	19980529
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5945403		A	19990831	US 1997-866735	19970530
AU 9877049		A1	19981230	AU 1998-77049	19980529
AU 744671		B2	20020228		
EP 996632		A1	20000503	EP 1998-925007	19980529
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001506506		T2	20010522	JP 1999-500952	19980529
US 2004002459		A1	20040101	US 2003-402364	20030328
PRIORITY APPLN. INFO.:				US 1997-866735	A 19970530
				WO 1998-US10979	W 19980529
				US 1999-309821	B1 19990511
				US 2001-761120	B1 20010116

AB Fragments of an endothelial cell proliferation inhibitor and method of use therefor are provided. The endothelial proliferation inhibitor is a protein derived from **plasminogen**, or more specifically is an angiostatin fragment. The angiostatin fragments generally correspond to **kringle** structures occurring within the endothelial cell proliferation inhibitor. The endothelial cell inhibiting activity of these fragments provides a means for inhibiting angiogenesis of tumors and for treating angiogenic-mediated disease.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 26 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:728577 HCAPLUS
DOCUMENT NUMBER: 130:485
TITLE: Adenovirus-mediated intratumoral delivery of an angiogenesis antagonist for the treatment of tumors
INVENTOR(S): Li, Hong; Lu, He; Griscelli, Franc; Opolon, Paule; Soria, Claudine; Ragot, Thierry; Legrand, Yves; Soria, Jeannette; Mabilat, Christelle; Perricaudet, Michel; Yeh, Patrice
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S.A., Fr.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9849321	A2	19981105	WO 1998-EP2491	19980427
WO 9849321	A3	19990225		
W:	AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			

AU 9879096	A1	19981124	AU 1998-79096	19980427
AU 753781	B2	20021031		
EP 979290	A2	20000216	EP 1998-929267	19980427
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI				
BR 9808697	A	20000711	BR 1998-8697	19980427
JP 2001523103	T2	20011120	JP 1998-546600	19980427
MX 9909594	A	20000630	MX 1999-9594	19991019
NO 9905242	A	19991227	NO 1999-5242	19991027
US 6638502	B1	20031028	US 2000-403736	20000629
PRIORITY APPLN. INFO.:			US 1997-44980P P	19970428
			WO 1998-EP2491 W	19980427

AB A method for gene therapy of tumors that inhibits angiogenesis is described. A gene encoding an anti-angiogenic factor is introduced into tumor cells, for example with a defective adenovirus vector, to inhibit growth or **metastasis**, or both, of the tumor. Specifically, a defective adenovirus that carrying an expression cassette for the amino terminal fragment of urokinase (ATF) inhibited growth and **metastasis** of tumors. These effects were correlated with a remarkable inhibition of neovascularization within, and at the immediate vicinity of, the injection site. Delivery of a defective adenovirus vector that expresses **kringles** 1 to 3 of angiostatin inhibited tumor growth and tumorigenicity, and induced apoptosis of tumor cells. The invention further provides viral vectors for use in the methods of the invention.

L30 ANSWER 27 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:725652 HCAPLUS
DOCUMENT NUMBER: 130:108418
TITLE: Cloning and functional characterization of a new phosphatidyl-inositol anchored molecule of a **metastasizing** rat pancreatic tumor
AUTHOR(S): Rosel, Marc; Claas, Christoph; Seiter, Simone; Herlevsen, Mikael; Zoller, Margot
CORPORATE SOURCE: Department of Tumor Progression and Immune Defense, German Cancer Research Center, Heidelberg, 69120, Germany
SOURCE: Oncogene (1998), 17(15), 1989-2002
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have described recently a panel of **metastasis** -associated antigens expressed on a rat pancreatic tumor. One of these mols., recognized by the monoclonal antibody C4.4 and named accordingly C4.4A, was under physiol. conditions expressed only in the gravid uterus and on epithelial of the upper gastrointestinal tract. The cDNA of the antigen has been **isolated** and cloned. The 1,637 b cDNA codes for a 352 amino acid long glycosylphosphatidyl-inositol (GP) anchored mol., whose mol. weight varies in different cells between 94-98 kDa according to the degree of N- and O-**glycosylation.** Data base searches have revealed a low degree of homol. to the receptor for the **plasminogen** activator (uPAR). After intrafootpad and i.v. application of C4.4A transfected and mock-transfected tumor cells, an increased number of **lung** nodules was detected with the former, whereby the individual **metastatic** nodules amalgamated without any encapsulation of the tumor tissue. Furthermore, C4.4A is involved in adhesion to laminin and, although transfection of a non-**metastasizing** tumor line with the mol. was not sufficient, constitutively C4.4A-pos. tumor cells penetrated through matrigel. This

process could be completely prevented by C4.4. Finally, the authors could demonstrate that uPA, albeit weakly, **bound** to the C4.4A mol. In view of the observed influence of C4.4A on **metastasis** formation and matrix penetration it is tempting to speculate that this newly described **metastasis**-associated mol. may exert functional activity similar to the uPAR, i.e. via activation of matrix degrading enzymes. By the very restricted expression of the mol. in the adult organism, modulation of C4.4A could well be of therapeutic interest.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 28 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:545400 HCAPLUS
DOCUMENT NUMBER: 129:170983
TITLE: sequence of mouse angiostatin protein with detection methods and applications to inhibit endothelial cell proliferation and cancer
INVENTOR(S): O'Reilly, Michael S.; Folkman, M. Judah
PATENT ASSIGNEE(S): The Children's Medical Center Corp., USA
SOURCE: U.S., 39 pp., Cont.-in-part of U. S. 5,639,725.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5792845	A	19980811	US 1994-326785	19941020
US 5639725	A	19970617	US 1994-248629	19940426
CA 2188813	AA	19951102	CA 1995-2188813	19950426
WO 9529242	A1	19951102	WO 1995-US5107	19950426
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9524617	A1	19951116	AU 1995-24617	19950426
AU 692865	B2	19980618		
ZA 9503419	A	19960111	ZA 1995-3419	19950426
EP 758390	A1	19970219	EP 1995-918854	19950426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1149319	A	19970507	CN 1995-193293	19950426
HU 76095	A2	19970630	HU 1996-2952	19950426
BR 9507479	A	19970916	BR 1995-7479	19950426
JP 09512173	T2	19971209	JP 1995-527831	19950426
US 5885795	A	19990323	US 1995-429743	19950426
US 5733876	A	19980331	US 1995-451932	19950526
US 5776704	A	19980707	US 1995-452260	19950526
US 2003064926	A1	20030403	US 2002-127066	20020422
US 2004023877	A1	20040205	US 2003-401108	20030327

PRIORITY APPLN. INFO.:

US 1994-248629	A2	19940426
US 1994-326785	A	19941020
US 1995-429743	A2	19950426
WO 1995-US5107	W	19950426
US 1996-612788	A3	19960308
US 1997-866735	A3	19970530
US 1997-989477	B2	19971212

US 1998-66028	A3	19980424
US 1999-309821	B1	19990511
US 1999-335325	A1	19990617
US 1999-338387	B1	19990622
US 2001-788142	A2	20010216

AB The endothelial inhibitor is a protein **isolated** from the blood or urine that is eluted as a single peak from C4-reverse phase high performance liquid chromatog. The endothelial inhibitor is a mol. comprising a protein having a mol. weight of between approx. 38 kilodaltons and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis and having an amino acid sequence substantially similar to that of a murine **plasminogen** fragment beginning at amino acid number 98 of a murine **plasminogen** mol. Diagnostic assays and kits for angiostatin measurement, and histochem. kits for localization of angiostatin, and mol. probes to monitor angiostatin biosynthesis, and antibodies specific for angiostatin are all described.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 29 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:529705 HCAPLUS

TITLE: Fragments of angiostatin protein and **plasminogen** as inhibitors of B16 melanoma **metastases.**

AUTHOR(S): Grella, Davida K.; Fogler, William E.; Chang, Amy; Plum, Stacy M.; Liang, Hong; Chang, Yuan; Wang, Hui; McCance, Stephen G.; Castellino, Francis J.; Sim, B. Kim Lee

CORPORATE SOURCE: University Notre Dame, Notre Dame, IN, 46556, USA

SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), MEDI-220. American Chemical Society: Washington, D. C.
CODEN: 66KYA2

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Angiostatin protein is identified as an internal fragment of **plasminogen**, containing the first four **kringle** domains (K1-4) and is a potent inhibitor of angiogenesis. Recent evidence demonstrates that K1-3 is also a potent angiogenic inhibitor. Individual **kringles** of **plasminogen** have varying degrees of anti-proliferative or anti-migratory effects. However, the ability of these fragments to inhibit tumor growth and **metastases** has not been determined In this study, we report the significance of these fragments to markedly reduce the number of **metastatic** tumors in murine **lungs.** Fragments K1-4, K1-3, K1-3 without N-linked **glycosylation**, K1-3 without the **interkringle** disulfide bond, K2-3, K2-3 without the **interkringle** disulfide bond, K2-3 without N-linked **glycosylation**, K4-5, K1, K4, K5, and K2 of tPA will be discussed.

L30 ANSWER 30 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:239304 HCAPLUS

DOCUMENT NUMBER: 128:294008

TITLE: Fragments of **plasminogen** effective in inhibiting tumor **metastasis** and growth and process for preparing the same

INVENTOR(S): **Morikawa, Wataru**; Miyamoto, Seiji

PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan; Morikawa, Wataru; Miyamoto, Seiji

SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815643	A1	19980416	WO 1997-JP3635	19971009
W: AU, CA, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 10114796	A2	19980506	JP 1996-287651	19961009
AU 9745714	A1	19980505	AU 1997-45714	19971009
US 2002031518	A1	20020314	US 2001-989388	20011121

PRIORITY APPLN. INFO.: JP 1996-287651 A 19961009
WO 1997-JP3635 W 19971009
US 1999-269720 A1 19990406

AB Fragments of a **plasminogen** effective in inhibiting tumor **metastasis** and growth, an enzymic process for preparing the fragments, and a tumor **metastasis** and growth inhibitor containing the fragments as the active ingredient are presented. The fragments are obtained from the **elastase**-induced hydrolysis product of **Lys-plasminogen** that is obtained by treating a **plasminogen** with plasmin and that preferably has a potent **heparin-binding** activity. Alternatively, the **Lys-plasminogen** is prepared by **autolysis** of **plasminogen** in the presence of **tranexamic acid** . The inhibitor is useful for clin. therapy of solid cancers typified by **lung** and colon cancers.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 31 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:430517 HCAPLUS
DOCUMENT NUMBER: 127:159807
TITLE: Increased expression of low density lipoprotein receptor-related protein/α2-macroglobulin receptor in human malignant astrocytomas
AUTHOR(S): Yamamoto, Masaaki; Ikeda, Kohichi; Ohshima, Kohichi; Tsugu, Hitoshi; Kimura, Hideo; Tomonaga, Masamichi
CORPORATE SOURCE: Department Neurosurgery, Fukuoka University School Medicine, Fukuoka, 814-01, Japan
SOURCE: Cancer Research (1997), 57(13), 2799-2805
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Low-d. lipoprotein receptor-related protein (LRP) plays an important role in regulating proteinase activity, which is necessary for cellular invasive processes. In this study, the authors investigated the presence of both LRP and urokinase-type **plasminogen** activator receptor (uPAR) in astrocytoma tissues and in glioma cell lines by PCR and immunohistochem. anal. LRP mRNA was expressed frequently in glioblastomas, as compared with low-grade astrocytomas by PCR anal. and was well correlated with uPAR expression. These results were consistent with the immunohistochem. localization of LRP in glioblastomas. Immunohistochem. of LRP on sequential frozen sections showed that neoplastic glial cells and **endothelial cells** of glioblastomas exhibited intense LRP immunoreactivity, whereas LRP was

almost undetectable in low-grade astrocytomas and in normal glial cells and **endothelial cells** of normal brain tissues. In normal brain tissues, LRP immunoreactivity was identified in the pyramidal neurons of the cerebral cortex. In **metastatic** brain tumors (**metastatic lung** adenocarcinomas) and primary **lung** adenocarcinomas, LRP expression was low to undetectable, suggesting that LRP expression is regulated differently in these tumors than in malignant astrocytomas. These results indicate that LRP is overexpressed in malignant astrocytomas, especially in glioblastomas, and the increased expression of LRP appears to correlate with the expression of uPAR and the malignancy of astrocytomas. The authors' results suggest strongly that LRP may play a role in facilitating glioblastoma invasiveness and neovascularization within tumor tissues by regulating cell surface proteolytic activity.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 32 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:301011 HCAPLUS
DOCUMENT NUMBER: 126:341822
TITLE: Role of type 1 **plasminogen** activator inhibitor (PAI-1) in **metastasis** formation of human fibrosarcoma (HT-1080)
AUTHOR(S): Matsuda, Eizo
CORPORATE SOURCE: Department Orthopaedic Surgery, School Medicine, Kanazawa University, Kanazawa, 920, Japan
SOURCE: Kanazawa Daigaku Juzen Igakkai Zasshi (1996), 105(6), 736-744
CODEN: JUZIAG; ISSN: 0022-7226
PUBLISHER: Juzen Igakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Monoclonal cell lines from human fibrosarcoma (HT-1080) parental cell line were established using the limited dilution method, and were subsequently screened for levels of type 1-**plasminogen** activator inhibitor (PAI-1) antigen. **Metastatic** potentials were evaluated by counting **metastatic** colonies formed on nude mice **lungs** after tumor cell inoculation, and the correlation between PAI-1 levels and **metastatic** potentials was investigated. Each fibrinolytic parameter was measured using an ELISA. Four monoclonal cell lines exhibiting stable levels of PAI-1 and urokinase-type **plasminogen** activator (u-PA) were used for the present study. Their tissue factor (TF) activity was evaluated on the cell surface by measuring prothrombin complex formation and chromogenic substrate conversion. MRNA levels of PAI-1 and u-PA were consistent with antigen levels. There was a highly significant difference in **metastatic** potentials as evaluated by counting **metastatic** colonies in nude mice **lungs** at 3 wk after the tail vein injection of the resp. tumor cells. **Metastatic** potentials significantly correlated with PAI-1 and TF levels. A clone with higher **metastatic** potential was not superior to one with lower **metastatic** potential, with regard to adhesiveness to endothelial cells. However, as compared with other clones, the clone with higher **metastatic** potential could stay in the **lung** longer after attachment. Regarding invasive potential into the extracellular matrix subsequent to the tumor cell's lodgement, no significant difference was observed between clones. To dissolve tumor thrombus (which is thought to be essential for the tumor cell's lodgement), nude mice were treated with **heparin** after tumor cell inoculation. No statistical effect was seen in mice inoculated with tumor cells exhibiting low PAI-1 and low TF. Lodgement in the **lung** 48

h after inoculation was significantly inhibited and the number of pulmonary **metastatic** colonies was reduced in tumor cells with high PAI-1 and high TF. Similar results were seen when mice were treated with anti-PAI-1 monoclonal antibody which inhibits PAI-1 activity. The data indicate that both PAI-1 expression and TF expression are crucial to **metastatic** potential of this tumor cell line and that inhibition of either PAI-1 or TF activity can prohibit formation of **lung metastases.**

L30 ANSWER 33 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:227357 HCAPLUS
DOCUMENT NUMBER: 126:302053
TITLE: A recombinant human angiostatin protein inhibits experimental primary and **metastatic** cancer
AUTHOR(S): Sim, B. Kim Lee; O'Reilly, Michael S.; Liang, Hong; Fortier, Anne H.; He, Weixuan; Madsen, John W.; Lapcevich, Randall; Nacy, Carol A.
CORPORATE SOURCE: EntreMed, Inc., Rockville, MD, 20850, USA
SOURCE: Cancer Research (1997), 57(7), 1329-1334
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endogenous murine angiostatin, identified as an internal fragment of **plasminogen**, blocks neovascularization and growth of exptl. primary and **metastatic** tumors in vivo. A recombinant protein comprising **kringles** 1-4 of human **plasminogen** (amino acids 93-470) expressed in Pichia pastoris had phys. properties (mol. size, **binding** to lysine, reactivity with antibody to **kringles** 1-3) that mimicked native angiostatin. This recombinant angiostatin protein inhibited the proliferation of bovine capillary **endothelial cells** in vitro. Systemic administration of recombinant angiostatin protein at doses of 1.5 mg/kg suppressed the growth of Lewis **lung** carcinoma-low **metastatic** phenotype **metastases** in C57BL/6 mice by greater than 90%; administration of the recombinant protein at doses of 100 mg/kg also suppressed the growth of primary Lewis **lung** carcinoma-low **metastatic** phenotype tumors. These findings demonstrate unambiguously that the antiangiogenic and antitumor activity of endogenous angiostatin residues with **kringles** 1-4 of **plasminogen.**

L30 ANSWER 34 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:281617 HCAPLUS
DOCUMENT NUMBER: 122:71492
TITLE: Inhibitory effect of oversulfated fucoidan on invasion through reconstituted basement membrane by murine Lewis **lung** carcinoma
AUTHOR(S): Soeda, Shinji; Ishida, Satoshi; Shimeno, Hiroshi; Nagamatsu, Atsuo
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, 814-80, Japan
SOURCE: Japanese Journal of Cancer Research (1994), 85(11), 1144-50
CODEN: JJCREP; ISSN: 0910-5050
PUBLISHER: Japanese Cancer Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of native, oversulfated, and desulfated fucoidans and **heparin** on the invasion of 3 LL cells through Matrigel (model basement membrane) were investigated. Of the 4 polysaccharides tested, oversulfated fucoidan was the most potent inhibitor of tumor cell invasion

and inhibited most potently and specifically the tumor cell adhesion to laminin. SDS-polyacrylamide gel electrophoretic anal. of the **binding** of **elastase**-cleaved laminin to fucosidan- and **heparin**-Sepharoses showed that both polysaccharides **bound** to the 62- and 56-kDa fragments. Pretreatments of 3 LL cells with native or oversulfated fucoidan reduced their adhesive potency to laminin. The 2 fucoidans further inhibited the laminin **binding** of 3 LL cells which had been pretreated with a laminin-based pentapeptide, YIGSR. These results suggest that fucoidan specifically **binds** not only to the **heparin binding** domain(s) of laminin but also to site(s) other than the cell surface laminin receptor. 3 LL cells secreted a 50-kDa form of urokinase-type **plasminogen** activator (u-PA). The extracellular level of u-PA activity was increased 1.7-fold by addition of laminin but not type IV collagen. Oversulfated fucoidan most potently reduced the increased u-PA levels. Therefore, the reduction in in vitro invasiveness of 3 LL cells by either fucoidan or its oversulfated derivative may result from an inhibition of phys. interaction between the tumor cells and the Matrigel (laminin), followed by a suppression of the laminin-induced increase in extracellular u-PA.

L30 ANSWER 35 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:601983 HCAPLUS
DOCUMENT NUMBER: 121:201983
TITLE: Inhibition of **metastasis** of Lewis **lung** carcinoma by a synthetic peptide within growth factor-like domain of urokinase in the experimental and spontaneous **metastasis** model
AUTHOR(S): Kobayashi, Hiroshi; Gotoh, Junko; Fujie, Michio; Shinohara, Hiromitsu; Moniwa, Nobuhiko; Terao, Toshihiko
CORPORATE SOURCE: Department Obstetrics and Gynecology, Hamamatsu University School Medicine, Hamamatsu, 431-31, Japan
SOURCE: International Journal of Cancer (1994), 57(5), 727-33
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Four synthetic peptides (residues 20-30 and 17-34) within the growth factor-like domain (GFD) of murine and human urokinase-type **plasminogen** activator (uPA) were examined to determine whether they inhibit production of exptl. and spontaneous **lung metastasis** by murine Lewis **lung** carcinoma (3LL) cells. In an in vivo exptl. **metastasis** assay, which dets. mainly the later steps of the **metastatic** migration process (extravasation from the bloodstream and then growth into pulmonary tumor), none of the peptides introduced by i.v. single co-injection into syngeneic C57B1/6 mice inhibited pulmonary **metastasis**, when 3LL cells were pre-**incubated** with the peptides followed by i.v. co-injection of the peptide and cells. In addition, none of the peptides, when injected i.p. daily for 7 days after i.v. tumor cell inoculation, reduced the number of **lung** tumor colonies. In a second in vivo assay that measures **metastasis** from a primary tumor (spontaneous **metastasis** model), multiple i.p. injections of the mouse peptide 17-34 for 7 days after s.c. tumor cell inoculation significantly inhibited **metastatic lung** tumor colonization in a dose-dependent manner, whereas human peptide 17-34 had no effect. Mouse and human peptide 20-30 had no effect either. The inhibition of **lung metastasis** was not due to direct antitumor effects of mouse peptide 17-34. Our results indicate that occupation of uPA receptors on 3LL cells by the enzymically inactive mouse peptide 17-34 or prevention of

rebinding of uPA synthesized by tumor cells to their receptor specifically reduced tumor cell invasion and formation of **metastasis** and that uPA may regulate more efficiently the mechanism involved in the entry of tumor cells into vascular circulation than extravasation during the **metastatic** process.

L30 ANSWER 36 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:469174 HCAPLUS
DOCUMENT NUMBER: 119:69174
TITLE: Tetranectin, a **plasminogen kringle** 4-**binding** protein. Cloning and gene expression pattern in human colon cancer
AUTHOR(S): Wewer, Ulla M.; Albrechtsen, Reidar
CORPORATE SOURCE: Lab. Mol. Pathol., Univ. Inst. Pathol. Anat., Copenhagen, Den.
SOURCE: Laboratory Investigation (1992), 67(2), 253-62
CODEN: LAINAW; ISSN: 0023-6837
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetranectin is a recently discovered protein that **binds** to **kringle** 4 region of **plasminogen.** The mRNA encoding human tetranectin was cloned by using degenerate primers in a reverse transcriptase reaction followed by polymerase chain reaction amplification. The resulting polymerase chain reaction product was examined by DNA sequencing and subsequently used as probe for screening a human placental cDNA library. A full-length cDNA clone (TET-1) was **isolated**, characterized, and used for Northern blot and in situ hybridization. DNA sequencing anal. revealed a 874-base pair cDNA containing an open reading frame of 606 base pairs encoding 202 amino acids. A classical signal peptide was present starting with the initiation methionine. The mature tetranectin chain consisted of 181 amino acids (Mr = 20,169). The 3' nonencoding region contained a single polyadenylation signal and a 26-residue poly A tail. The predicted amino acid sequence of the mature tetranectin chain showed, except for one amino acid, complete identity to that obtained by sequencing of the native protein. Northern blot of poly A+ revealed a single band of .apprx.1 kb. Northern blot anal. of poly A+ **isolated** from a series of normal human tissues (**lung**, liver, spleen, kidney, and pancreas) revealed a distinct hybridization band that was especially prominent in the **lungs** and spleen. No hybridization signal was detected in three carcinoma cell lines examined in parallel. Northern blot anal. of poly A+ RNA **isolated** from solid tumors revealed a tetranectin-specific mRNA band. In situ hybridizations on tissue sections of colon carcinomas and normal colon tissues revealed a strong and distinct hybridization signal of stroma cells in colon carcinomas but not in tumor cells. Only a few stromal cells were labeled in the normal colon. Immunohistochem., tetranectin was found in a fibrillar-like pattern in the extracellular matrix around the tumor islands and was not detectable in the normal colon stromal tissue. **Plasminogen** exhibited a similar immunohistochem. staining pattern as tetranectin. Human tetranectin cDNA comprises 874 base pairs including a 606-base pair open reading frame encoding 202 amino acids including a classical signal peptide. This protein is produced locally by cells of the stromal compartment of tumors and is deposited into the extracellular matrix. Since tetranectin **binds** to **plasminogen** the authors hypothesize that it could function as an anchor and/or reservoir for **plasminogen** and similar substances that regulate tumor invasion, **metastasis**, and angiogenesis.

L30 ANSWER 37 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:40188 HCAPLUS
DOCUMENT NUMBER: 114:40188
TITLE: Relationship between secreted urokinase **plasminogen** activator activity and **metastatic** potential in murine B16 cells transfected with human urokinase sense and antisense genes
AUTHOR(S): Yu, Heron; Schultz, Richard M.
CORPORATE SOURCE: Stritch Sch. Med., Loyola Univ. Chicago, Maywood, IL, 60153, USA
SOURCE: Cancer Research (1990), 50(23), 7623-33
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Murine melanoma B16-F1 cells of low **metastatic** potential were transfected with the human gene for the prepro-form of urokinase in an SV40 expression vector (plasmid pSV2-uPA), and cells expressing high amts. of the human urokinase gene product were selected for by an ELISA specific for human high mol. weight urokinase. Southern anal. showed one of the cell lines (clone 7) had incorporated 150 copies of the pSV2-uPA plasmid into its genomic DNA. The human urokinase synthesized by the pSV2-uPA-transfected murine B16 cells was found to be **glycosylated** and did not **bind** to the murine cell surface urokinase receptor sites. In an in vivo assay that measures **metastasis** from a primary tumor (spontaneous **metastatic** assay), clone 7 cells showed an increased ability to **metastasize** (12 of 12 mice showed **metastatic** tumors), while control cells showed a lower ability to **metastasize** (only 2 of 11 mice showed **metastatic** tumors). In a second in vivo assay, which measures only the steps of the **metastatic** migration process during which tumor cells extravasate from the blood and then grow into pulmonary tumors (**lung** colonization assay), a significant multifold increase in the ability to form **lung** tumors was shown by the high human urokinase-secreting B16-F1 cells. In B16-F10 cells incorporating an antisense sequence to preprourokinase (plasmid pSV2-ASuPA-265) and secreting significantly decreased amts. of murine urokinase, a corresponding significant decrease in **lung** colonization was observed These results provide direct exptl. support for a role of secreted (non-surface-**bound**) urokinase in the colonization steps of the **metastatic** process. Furthermore, the data indicate that the higher **lung** colonization ability of the B16-F10 line than of the B16-F1 line is primarily based on the quant. differences in their abilities to produce urokinase.

L30 ANSWER 38 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:22375 HCAPLUS
DOCUMENT NUMBER: 114:22375
TITLE: Interleukin-4 (IL-4) in method and compositions for degradation and prevention of fibrin deposits associated with pathological conditions
INVENTOR(S): Hamilton, John Allan; Hart, Prudence Hamilton
PATENT ASSIGNEE(S): University of Melbourne, Australia
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9007932	A1	19900726	WO 1990-AU13	19900119
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
CA 2045574	AA	19900721	CA 1990-2045574	19900119
AU 9049645	A1	19900813	AU 1990-49645	19900119
AU 639903	B2	19930812		
EP 454736	A1	19911106	EP 1990-902120	19900119
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 04503062	T2	19920604	JP 1990-502488	19900119
JP 06011706	B4	19940216		
US 5236705	A	19930817	US 1991-720868	19910918
PRIORITY APPLN. INFO.:			AU 1989-2356	19890120
			WO 1990-AU13	19900119

AB A method for degrading fibrin deposits and preventing such deposits associated with pathol. conditions comprises administration of a therapeutically effective amount of IL-4, or a derivative thereof having IL-4 activity, optionally in association with ≥1 pharmaceutically acceptable **carriers** or excipients. IL-4-containing thrombolytic compns. are disclosed. Thus, IL-4 stimulated production of tissue **plasminogen** activator (tPA) in human monocytes, stimulated PA activity in bovine aortic endothelial cells, and inhibited procoagulant activity in human monocytes.

L30 ANSWER 39 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1986:146384 HCAPLUS
DOCUMENT NUMBER: 104:146384
TITLE: Effect of butyric acid on **lung**-colonizing ability of cloned low-**metastatic** Lewis **lung** carcinoma cells
AUTHOR(S): Takenaga, Keizo
CORPORATE SOURCE: Dep. Chemother., Chiba Cancer Cent. Res. Inst., Chiba, 280, Japan
SOURCE: Cancer Research (1986), 46(3), 1244-9
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

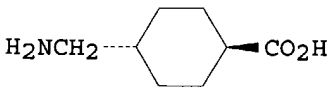
AB The **lung**-colonizing ability of low-**metastatic** Lewis **lung** carcinoma cells (P-29) was enhanced by their in vitro treatment with butyric acid and Na butyrate. Of the short chain fatty acids tested, butyric acid was the most effective in enhancing the **lung**-colonizing ability of P-29 cells; **propionic** acid and valeric acid were slightly effective, but acetic acid and caproic acid were ineffective. The enhancing effect of butyric acid on the **lung**-colonizing ability of P-29 cells was reversible, indicating that the result was the consequence of epigenetic alterations. Treatment of P-29 cells with butyric acid resulted in enhancement of secretion of **plasminogen** activator, cellular cathepsin B activity, and cellular adhesiveness. The phenotypes of cells treated with butyric acid were compared with those of cells treated with DMSO which was reported to enhance the **lung**-colonizing ability of P-29 cells. Significant differences were found in the phenotypes, especially that of cellular adhesiveness; i.e., butyric acid enhanced mainly homotypic aggregation of the cells, whereas DMSO enhanced mainly heterotypic adhesion, such as adhesion to monolayers of endothelial cells. In addition, butyric acid reversibly caused hyperacetylation of core histones in P-29 cells, whereas DMSO did not.

L30 ANSWER 40 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1982:574645 HCAPLUS
DOCUMENT NUMBER: 97:174645

TITLE: Ultrastructural study of the effects of **tranexamic acid** and urokinase on **metastasis** of Lewis **lung** carcinoma
AUTHOR(S): Tanaka, N.; Ogawa, H.; Kinjo, M.; Kohga, S.; Tanaka, K.
CORPORATE SOURCE: Dep. Pathol., Daiichi Seiyaku Co., Tokyo, 134, Japan
SOURCE: British Journal of Cancer (1982), 46(3), 428-35
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lewis **lung** carcinoma cells were implanted in the foot-pads of mice and the effects of the **plasminogen**-plasmin inhibitor **tranexamic acid** (t-AMCHA) [**1197-18-8**] and or the **plasminogen** activator urokinase [9039-53-6] on **metastasis** were examined by electron microscopy. The intravascular tumor cells were not associated with thrombus formation in either control or urokinase-treated mice. Polymerized fibrin deposition around tumor cells and thrombi composed of fibrin and platelets was observed only in the mice given t-AMCHA. This suggests that the inhibition of fibrinolysis by t-AMCHA caused fibrin deposition and thrombus formation around intravascular tumor cells, which prevented release of the cells from primary foci to form secondary tumors. On the other hand, fibrinolysis induced by urokinase prevented thrombus formation, and accelerated cell release from primary foci.

L30 ANSWER 41 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1982:174007 HCAPLUS
DOCUMENT NUMBER: 96:174007
TITLE: Effects of **tranexamic acid** and urokinase on hematogenous **metastases** of Lewis **lung** carcinoma in mice
AUTHOR(S): Tanaka, Noriko; Ogawa, Hidemasa; Tanaka, Kenzo; Kinjo, Mitsuru; Kohga, Shin
CORPORATE SOURCE: Res. Inst., Daiichi Seiyaku Co., Ltd., Tokyo, Japan
SOURCE: Invasion & Metastasis (1981), 1(3), 149-57
CODEN: INVMDJ; ISSN: 0251-1789
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB **tranexamic acid** (I) [**1197-18-8**] (a plasmin-**plasminogen** inhibitor) inhibited **metastases** formation in mice with s.c. implanted Lewis **lung** carcinoma, which has low thromboplastic and low fibrinolytic activities, whereas administration of urokinase [9039-53-6] (a **plasminogen** activator) enhanced pulmonary **metastases.** The effect of I appeared to be due to the prevention of tumor cell release from the implanted site and due to fibrin formation around tumor cells in the vessels of primary foci. Neither I nor urokinase had any effect on **metastases** in the **lung** of mice injected i.v. with Lewis **lung** carcinoma cells. The role of the coagulation-fibrinolysis system in tumor intravasation is discussed.

L30 ANSWER 42 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1967:103782 HCAPLUS
DOCUMENT NUMBER: 66:103782
TITLE: Effect of **heparin** and **plasminogen** inhibitor (EACA) in brief and prolonged treatment on intravenously injected tumor cells
AUTHOR(S): Boeryd, Bernt
CORPORATE SOURCE: Univ. Goteborg, Goteborg, Swed.
SOURCE: Acta Pathologica et Microbiologica Scandinavica (1966), 68(3), 347-54
CODEN: APMIAL; ISSN: 0365-5555
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Heparin** (I) (0.1 mg.), but not ε-aminocaproic acid (II) (30 mg.) injected intrajugularly into isologous mice promoted the transhepatic passage of intraportally inoculated tumor cells induced by 20-methylcholanthrene. I (1 mg. daily for 6 days) increased the incidence of **metastases** of i.v. injected tumor cells, but decreased the total **metastatic** volume in the **lungs**, and in the liver did not affect the incidence of **metastases**, but did increase the total **metastatic** volume II (30% of diet) failed to affect the incidence of **metastasis** of i.v. injected tumor cells in the **lungs** and liver, but increased the total **metastatic** volume in the **lungs**. Observations for 12 days after treatment indicated that anticoagulant therapy did not inhibit the incidence of **metastases** in isologous mice, and facilitated the dissemination of tumor cells into various organs. 22 references.

L30 ANSWER 43 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1967:103258 HCAPLUS
DOCUMENT NUMBER: 66:103258
TITLE: Effect of **heparin**, **plasminogen** inhibitor (EACA), and trauma on tumor **metastases**
AUTHOR(S): Boeryd, Bernt; Rudenstam, Carl M.
CORPORATE SOURCE: Univ. Goteborg, Goteborg, Swed.
SOURCE: Acta Pathologica et Microbiologica Scandinavica (1967), 69(1), 28-34
CODEN: APMIAL; ISSN: 0365-5555
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Trauma (bilateral crush fracture of the thighs) 1 hr. prior to the i.v. inoculation of CBA mice with MCG1 tumor cells increased the number and average and total vols. of **metastases** to the **lungs**, and decreased the number to the liver. **Heparin** (2 mg., s.c.) 2 hrs. before and 3 hrs. after the i.v. inoculation of C3H mice with spontaneous mammary cancer cells increased the number of **metastases** to the **lungs** and reduced their average volume, but the total volume was unchanged, as compared with controls. ε-Aminocaproic acid (EACA) (I) (30 mg., i.v.) 2 hrs. before and 1 and 4 hrs. after the mammary cancer cell injection increased the number and average and total vols. of **metastases** to the **lungs**, as compared with controls. Trauma increased the number and total volume of **metastases**, but left the average volume unchanged as compared with controls. When trauma and I treatment were combined, the number as well as the total volume of **metastases** to the **lungs** were further increased, but the average volume was not changed compared with controls. The effect of **heparin** might be due to transcapillary passage facilitation and repeated circulation of tumor cells. The effects of I and trauma on pulmonary **metastases** are probably due to the increased retention

of tumor cells in the **lungs**. 27 references.

L30 ANSWER 44 OF 44 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1966:70211 HCAPLUS
DOCUMENT NUMBER: 64:70211
ORIGINAL REFERENCE NO.: 64:13186f-g
TITLE: Action of **heparin** and a **plasminogen** inhibitor (EACA) on **metastatic** tumor spread in an isologous system
AUTHOR(S): Boeryd, Bernt
CORPORATE SOURCE: Univ. Goteborg, Swed.
SOURCE: Acta Pathologica et Microbiologica Scandinavica (1965), 65(3), 395-404
CODEN: APMIAL; ISSN: 0365-5555
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mice, pretreated with either an intraperitoneal injection of 0.05 ml. 1% **heparin** (I) or an intravenous injection of 0.1-0.2 ml. of 30% ε-aminocaproic acid (II), were inoculated intravenously with an enzymically prepared cell suspension (Madden and Burk, CA 56, 3987e) of a 20-methylcholanthrene-induced rhabdomyosarcoma MCG1 in an isologous system. I inhibited the number of pulmonary **metastases** and increased the number of liver **metastases**, while II decreased the number of liver **metastases** and increased the number and total volume of pulmonary **metastases**. Therefore, I and II seem essentially to affect transpulmonary passage of tumor cells; whereas I seemed to make the tumor cells more liable to pass the **lungs**, the results from the II-treated mice suggested that the main effect of inhibition of **plasminogen** activity is to reinforce the sieve action of the **lungs**, thereby retaining more cells there. Thrombosis does not seem to be essential for **metastatic** growth in this system. 36 references.

```
=> d que stat l32
L1            22 SEA FILE=HCAPLUS ABB=ON  ("MORIKAWA W"/AU OR "MORIKAWA
                 WATARU"/AU)
L10            1 SEA FILE=REGISTRY ABB=ON  PLASMINOGEN/CN
L11            1 SEA FILE=REGISTRY ABB=ON  LYS-PLASMINOGEN/CN
L12            1 SEA FILE=REGISTRY ABB=ON  ELASTASE/CN
L13            1 SEA FILE=REGISTRY ABB=ON  "TRANEXAMIC ACID"/CN
L14        25224 SEA FILE=HCAPLUS ABB=ON  L10 OR L11 OR ?PLASMINOGEN? OR
                 LYS?(W)?PLASMINOGEN?
L15         1448 SEA FILE=HCAPLUS ABB=ON  L14 AND ?METAST?
L16          281 SEA FILE=HCAPLUS ABB=ON  L15 AND (?LUNG? OR ?RESPIR?)
L17           16 SEA FILE=HCAPLUS ABB=ON  L16 AND ?KRINGLE?
L18           11 SEA FILE=HCAPLUS ABB=ON  L16 AND (L1 OR ?HEPARIN?)
L19            9 SEA FILE=HCAPLUS ABB=ON  L16 AND (N(W)?TERMINAL? OR ?GLYCOSYLAT
                 ?)
L21            3 SEA FILE=HCAPLUS ABB=ON  L16 AND ?IONIC?
L22            8 SEA FILE=HCAPLUS ABB=ON  L16 AND (?ENDOTHEL?(W)?CELLS AND
                 ?BLOOD?(W)?VESSEL?)
L24            5 SEA FILE=HCAPLUS ABB=ON  L16 AND ?INCUBAT?
L25            3 SEA FILE=HCAPLUS ABB=ON  L16 AND (L13 OR ?TRANEXAMIC?(W)?ACID)

L26           44 SEA FILE=HCAPLUS ABB=ON  L17 OR L18 OR L19 OR L21 OR L22 OR
                 L24 OR L25
L27            9 SEA FILE=HCAPLUS ABB=ON  L26 AND (?AUTOLYS? OR L12 OR ?ELASTAS?
                  OR ?FRACTION?)
L28           20 SEA FILE=HCAPLUS ABB=ON  L26 AND (?IDENTIFY? OR ?ISOLAT? OR
                 ?BIND? OR ?BOUND?)
L29            3 SEA FILE=HCAPLUS ABB=ON  L26 AND ?CARRIER?
L30           44 SEA FILE=HCAPLUS ABB=ON  L26 OR L27 OR L28 OR L29
L31          105 SEA L30
L32           60 DUP REMOV L31 (45 DUPLICATES REMOVED)

=> d ibib abs l32 1-60

L32  ANSWER 1 OF 60  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:    2004150099  EMBASE
TITLE:               Superior vena cava syndrome during chemotherapy for stage
                     3c fallopian tube adenocarcinoma.
AUTHOR:              Griffin D.; Martino M.A.; Hoffman M.S.
CORPORATE SOURCE:    D. Griffin, Dept. of Obstetrics and Gynecology, School of
                     Medicine, Wake Forest University, Medical Center Boulevard,
                     Winston-Salem, NC 27157-1065, United States.
                     dgriffin@wfubmc.edu
SOURCE:              Gynecologic Oncology, (2004) 93/1 (257-259).
                     Refs: 10
                     ISSN: 0090-8258  CODEN: GYNOA3
PUBLISHER IDENT.:    S 0090-8258(03)00874-6
COUNTRY:             United States
DOCUMENT TYPE:       Journal; Article
FILE SEGMENT:        010     Obstetrics and Gynecology
                     015     Chest Diseases, Thoracic Surgery and Tuberculosis
                     016     Cancer
                     018     Cardiovascular Diseases and Cardiovascular Surgery
                     037     Drug Literature Index
LANGUAGE:            English
SUMMARY LANGUAGE:    English
AB   Background. Superior vena cava syndrome is most often encountered in
     patients with malignancies. The diagnosis constitutes an oncologic
     emergency with prompt treatment indicated to manage the acute symptoms.
```

There are few reports describing the syndrome in patients with gynecologic malignancies and central venous catheters. Management has included treatment of the **metastatic** disease and anticoagulation/thrombolysis with catheter removal early in therapy. Case report. The case described is the first report of a patient with fallopian tube carcinoma complicated by SVC syndrome. The complication was attributed to an implanted venous access port being utilized to give adjuvant combination chemotherapy. Conclusion. Superior vena cava syndrome is rarely encountered in gynecologic oncology patients and constitutes a medical emergency. When encountered in the setting of an implanted catheter, thrombolysis and anticoagulation is an alternative to catheter removal in selected patients. .COPYRGT. 2004 Elsevier Inc. All rights reserved.

L32 ANSWER 2 OF 60 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 1040147787 JICST-EPlus
TITLE: Pulmonary Embolism Caused by Liposarcoma of the Thigh : Case Report
AUTHOR: MORIYA KOJI
INOUE ZEN'YA; SAITO HIDEHIKO; NAGANO JUNJI
CORPORATE SOURCE: Tachikawasogobyoin Seikeigeka
Seirei Hamamatsu Hospital, JPN
SOURCE: Rinsho Seikei Geka (Clinical Orthopaedic Surgery), (2004) vol. 39, no. 2, pp. 229-232. Journal Code: Z0276A (Fig. 5, Ref. 6)
ISSN: 0557-0433
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Short Communication
LANGUAGE: Japanese
STATUS: New
AB Rare case contracted serious pulmonary embolism is reported due to thrombus formed by compressed an enormous femoral vein. Patient is a 61-year-old woman, and the chief complaint is dyspnea. She has medical examination in an emergency visit. She is diagnosed as a multiple pulmonary embolism by chest radiography, blood gas view, electrocardiography, heart echo and scintigraphy. **Heparin** is administered for thrombolytic therapy and urokinase is administered for the prevention of thrombosis. MRI view, gadolinium MRI, operation view and histopathological opinion of the resected specimen are explained. Histological examination showed the tumor to be aliposarcoma. Postoperative radiation is also performed. Recurrence of **metastasis** is not revealed.

L32 ANSWER 3 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003503768 EMBASE
TITLE: Hemostatic regulators of tumor angiogenesis: A source of antiangiogenic agents for cancer treatment?.
AUTHOR: Daly M.E.; Makris A.; Reed M.; Lewis C.E.
CORPORATE SOURCE: Dr. C.E. Lewis, Academic Unit of Pathology, Sch. of Medicine/Biomedical Sciences, Beech Hill Rd., Sheffield S10 2RX, United Kingdom. Claire.lewis@sheffield.ac.uk
SOURCE: Journal of the National Cancer Institute, (19 Nov 2003) 95/22 (1660-1673).
Refs: 167
ISSN: 0027-8874 CODEN: JNCIAM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology

030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy

LANGUAGE: English
SUMMARY LANGUAGE: English

AB The maintenance of vascular integrity and control of blood loss are regulated by a sophisticated system of circulating and cell-associated hemostatic factors. These factors control local platelet aggregation, the conversion of soluble fibrinogen to an insoluble fibrin polymer, and the dissolution of fibrin. However, hemostatic factors are also involved in a number of physiologic processes, including development, tissue remodeling, wound repair, reproduction, inflammation, and angiogenesis. In this review, we outline ways in which angiogenesis is coordinated with and regulated by hemostasis. We focus on inhibitors of angiogenesis contained within platelets or harbored as cryptic fragments of hemostatic proteins and assess the experimental and preclinical evidence for their ability to inhibit tumor angiogenesis and, thus, their potential to be anticancer agents. Finally, we review the results of recent clinical trials involving angiogenesis inhibitors and the evidence that antiangiogenic therapy may be associated with hemostatic complications.

L32 ANSWER 4 OF 60 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003167073 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12684650
TITLE: Combined treatment with verapamil, a calcium channel blocker, and B428, a synthetic uPA inhibitor, impairs the **metastatic** ability of a murine mammary carcinoma.
AUTHOR: Todaro Laura B; Ladeda Virginia; Bal de Kier Joffe Elisa; Farias Eduardo F
CORPORATE SOURCE: Research Area, Angel H. Roffo Institute of Oncology, University of Buenos Aires, (C1417DTB) Buenos Aires, Argentina.
SOURCE: Oncology reports, (2003 May-Jun) 10 (3) 725-32. Journal code: 9422756. ISSN: 1021-335X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20030410
Last Updated on STN: 20031219
Entered Medline: 20031218

AB Urokinase **plasminogen** activator (uPA) and metalloproteinases (MMP) play key roles in invasion and **metastasis**, degrading extracellular matrix compounds and modulating tumor cell motility. Their regulation is an attractive therapeutic target for controlling tumor **metastasis.** Previously we have demonstrated that urokinase overexpression in murine mammary tumor cells is regulated by a Ca2+-dependent pathway and that blockage of Ca2+ channels by verapamil partially inhibited their invasive and **metastatic** ability. Moreover, the catalytic inhibition of uPA by a synthetic uPA inhibitor B428 reduced local tumor invasiveness but not tumor cell dissemination. We evaluated the effect of a combined treatment with verapamil and B428 on the murine mammary carcinoma F3II behavior in vivo and in vitro. In vivo administration of the combined treatment was not associated to an overt toxicity. Only the daily combined treatment, beginning after tumor take, reduced the incidence and the number of spontaneous **lung metastasis**, while no differences were found in the subcutaneous growth of the primary tumor. Interestingly, a remarkable reduction in

plasma MMP-9 activity was found associated to **metastasis** impairment. In addition, the number of experimental **lung metastases** was also significantly diminished, with respect to the control group, only when both compounds were co-administered daily, beginning three days after i.v. tumor cell injection. In vitro, both compounds, either separately or combined, could inhibit secreted uPA activity. F3II cell migration was significantly inhibited by **incubation** with 50 microM verapamil, 15 microM B428 or the co-treatment with 7.5 microM B428 + 25 microM verapamil. The cell spread was also significantly reduced when F3II cells were exposed to the compounds, with an additive effect when B428 + verapamil combination was used. The combination of two compounds acting through different molecular targets may be useful to improve the control of **metastatic** dissemination.

L32 ANSWER 5 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003354842 EMBASE
TITLE: Molecular targets in the inhibition of angiogenesis.
AUTHOR: Dudek A.Z.; Pawlak W.Z.; Kirstein Pharm M.N.
CORPORATE SOURCE: Dr. A.Z. Dudek, Div. of Hematol. Oncol./Transplant., Department of Medicine, Comprehensive Cancer Center, 420 Delaware Street, Minneapolis, MN 55455, United States. dudek002@umn.edu
SOURCE: Expert Opinion on Therapeutic Targets, (2003) 7/4 (527-541).
Refs: 190
ISSN: 1472-8222 CODEN: EOTTAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Angiogenesis, the process of blood vessel formation, is crucial for malignant tumour growth and **metastases**; therefore, it has become an attractive target for anticancer therapy. Theoretically applicable to most solid tumours, this therapy may be advantageous over existing cytotoxic therapy, since it is directed at genetically stable endothelium growing within tumours rather than at malignant cells, which acquire resistance to treatment. Many promising angiogenesis inhibitors have been developed, although their activity has yet to be demonstrated in human clinical trials. To improve therapeutic benefit, this may require further insight into tumour angiogenesis, development of appropriate surrogate markers of activity, treatment of early stage neoplastic disease and probably a combination of different classes of antiangiogenesis agents to overcome redundant mechanisms of angiogenesis control.

L32 ANSWER 6 OF 60 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2003408261 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12946315
TITLE: Coelectrotransfer to skeletal muscle of three plasmids coding for antiangiogenic factors and regulatory factors of the tetracycline-inducible system: tightly regulated expression, inhibition of transplanted tumor growth, and **antimetastatic** effect.

AUTHOR: Martel-Renoir Dominique; Trochon-Joseph Veronique; Galaup Ariane; Bouquet Celine; Griscelli Franck; Opolon Paule; Opolon David; Connault Elisabeth; Mir Lluis; Perricaudet Michel
CORPORATE SOURCE: Vectorologie et Transfert de Genes, UMR 8121, Institut Gustave Roussy, 39 Rue Camille Desmoulins, 94805, Villejuif, France.. renoir@igr.fr
SOURCE: Molecular therapy : journal of the American Society of Gene Therapy, (2003 Sep) 8 (3) 425-33.
Journal code: 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20030830
Last Updated on STN: 20040429
Entered Medline: 20040428

AB We describe an approach employing intramuscular plasmid electrotransfer to deliver secretable forms of K1-5 and K1-3-HSA (a fusion of K1-3 with human serum albumin), which span, respectively, five and three of the five **kringle** domains of **plasminogen.** A tetracycline-inducible system (Tet-On) composed of three plasmids coding, respectively, for the transgene, the tetracycline transcriptional activator rtTA, and the silencer tTS was employed. K1-3-HSA and K1-5, produced from C2C12 muscle cells, were found to inhibit endothelial cell (HMEC-1) proliferation by 30 and 51%, respectively. In vivo, the expression of the transgene upon doxycycline stimulation was rapid, stable, and tightly regulated (no background expression) and could be maintained for at least 3 months. Blood half-lives of 2.1 and 3.7 days were found for K1-5 and K1-3-HSA, respectively. The K1-5 protein was secreted from muscle into blood at a level of 45 ng/ml, which was sufficient to inhibit MDA-MB-231 tumor growth by 81% in nude mice and B16-F10 melanoma cell **lung** invasion in C57BL/6 mice by 73%. PECAM-1 immunostaining studies revealed modest tumor vasculature in mice expressing K1-5. In contrast, K1-3-HSA, although secreted into blood at much higher level (250 ng/ml) than K1-5, had no effect on tumor growth.

L32 ANSWER 7 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003259738 EMBASE
TITLE: Modulation of malignant growth by the coagulation mechanism and anticoagulants.
AUTHOR: Mammen E.F.
CORPORATE SOURCE: Dr. E.F. Mammen, Wayne Stt. Univ. School of Medicine, Detroit, MI, United States
SOURCE: Seminars in Thrombosis and Hemostasis, (2003) 29/3 (237-238).
ISSN: 0094-6176 CODEN: STHMBV
COUNTRY: United States
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English

L32 ANSWER 8 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003412381 EMBASE
TITLE: Cytosolic levels of neuron-specific enolase in squamous

cell carcinomas of the **lung.**

AUTHOR: Ruibal A.; Nunez M.I.; Rodriguez J.; Jimenez L.; Del Rio M.C.; Zapatero J.

CORPORATE SOURCE: Dr. A. Ruibal, Servicio de Medicina Nuclear, Hospital Clinico Universitario, Complejo Hospitalario Universitario, Edificio D, 15706 Santiago de Compostela, Spain. Alvaro.Ruibal.Morell@sergas.es

SOURCE: International Journal of Biological Markers, (2003) 18/3 (188-194).
Refs: 42
ISSN: 0393-6155 CODEN: IBMAEP

COUNTRY: Italy

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB To study the behavior and possible correlations of neuron-specific enolase (NSE) with other clinicobiological parameters, we measured the cytosolic levels of this marker by means of an immunoradiometric assay (IRMA) in 95 squamous cell **lung** carcinoma samples. We also analyzed the levels of pS2, tissue-type **plasminogen** activator (t-PA), hyaluronic acid (HA), free beta subunit of human **chorionic** gonadotropin (β-HCG), CYFRA 21.1 and CA 125 in cytosol. On the cell surface we analyzed the concentrations of epidermal growth factor receptor (EGFR), HA, erbB-2 oncoprotein, CD44s, CD44v5 and CD44v6. Other parameters considered were clinical stage, lymph node involvement, histological grade (HG), ploidy and the cellular S-phase **fraction** measured by flow cytometry on nuclei obtained from fresh tissues. In the 95 squamous cell carcinomas the cytosolic levels of NSE varied from 4.5 to 2235 ng/mg protein (median: 267) and were significantly higher ($p<0.001$) than those observed in 38 samples of normal pulmonary tissue obtained from the same patients (range: 56-657; median: 141.5). When classifying tumors according to the different parameters analyzed, we observed that the levels of NSE were higher in aneuploid than in diploid cases ($p=0.046$) and in those that were HG3 than in those that were HG2 ($p<0.001$). Tumors with high NSE levels (>422 ng/mg protein; 75th percentile) were more likely to have high S-phase values ($p=0.012$) and were more frequently aneyploid ($p=0.038$) and HG3 ($p<0.001$) than those with low levels of NSE (<180 ng/mg protein; 25th percentile). These results lead us to the following conclusions: 1) the cytosolic concentrations of NSE are significantly higher in squamous cell carcinomas than in healthy pulmonary tissue, and 2) the cytosolic concentrations of NSE are not correlated with clinical stage or nodal involvement. However, in our study higher levels of the enzyme were statistically correlated with aneuploidy, histological grade 3 and S-phase. This may explain its association with poorer outcome and progression, but also the more favorable response of tumors with elevated NSE to chemotherapy, as suggested by other groups.

L32 ANSWER 9 OF 60 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2002645788 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12405293

TITLE: Lovastatin alters cytoskeleton organization and inhibits experimental **metastasis** of mammary carcinoma cells.

AUTHOR: Farina Hernan G; Bublik Debora R; Alonso Daniel F; Gomez Daniel E

CORPORATE SOURCE: Laboratory of Molecular Oncology, Quilmes National

University, Bernal, Buenos Aires, Argentina..
hgfarina@unq.edu.ar
SOURCE: Clinical & experimental metastasis, (2002) 19 (6) 551-9.
Journal code: 8409970. ISSN: 0262-0898.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021031
Last Updated on STN: 20021211
Entered Medline: 20021120

AB Lovastatin is a competitive inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A reductase, the key regulatory enzyme of cholesterol biosynthesis. This enzyme catalyzes the formation of mevalonate, which is also the precursor of isoprenoid moieties, such as farnesol and geraniol, that are incorporated into several molecules essential for tumor cell signaling. Here, we describe that pretreatment with a non-cytotoxic concentration of lovastatin (10 microM) dramatically inhibited the **metastatic** ability of F311 mammary carcinoma cells in syngeneic BALB/c mice. Similarly, daily i.p. treatment of animals with a well-tolerated dose of lovastatin (10 mg/kg/day) significantly reduced the number of experimental **lung metastases.** In vitro, **incubation** of F3II monolayers in the presence of lovastatin caused a rounded-cell morphology. Immunofluorescence analysis revealed a lack of cortical actin organization, micrutubule disruption and inhibition of integrin-mediated focal contacts in lovastatin-treated cells. Exposure of F3II cells to lovastatin significantly inhibited tumor cell adhesion and migration, and **coincubation** with the cholesterol precursor mevalonate prevented these effects. Lovastatin reduced membrane localization of Rho protein, a signaling molecule involved in the regulation of actin-based cell motility that needs geranylation for membrane association and activation. In addition, lovastatin induced a dose-dependent inhibition in the secretion of urokinase, a key proteolytic enzyme during tumor invasion and **metastasis**, and a significant increase of tissue-type **plasminogen** activator, a marker of good prognosis in mammary cancer. These data suggest that **antimetastatic** properties of lovastatin are strongly associated with alterations in cytoskeleton organization and the consequent modulation of adhesion, motility and proteolysis.

L32 ANSWER 10 OF 60 EMBASE
on STN
ACCESSION NUMBER: 2003447844 EMBASE
TITLE: Angiogenesis modulation in cancer research: Novel clinical approaches.
AUTHOR: Cristofanilli M.; Charnsangavej C.; Hortobagyi G.N.
CORPORATE SOURCE: M. Cristofanilli, Dept. of Breast Medical Oncology, The University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, United States.
mcristof@mdanderson.org
SOURCE: Nature Reviews Drug Discovery, (2002) 1/6 (415-426).
Refs: 87
ISSN: 1474-1776 CODEN: NRDDAG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 014 Radiology
016 Cancer
021 Developmental Biology and Teratology
030 Pharmacology

037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Angiogenesis - the formation of new blood vessels - is essential for tumour progression and **metastasis.** Consequently, the modulation of tumour angiogenesis using novel agents has become a highly active area of investigation in cancer research, from the bench to the clinic. However, the great therapeutic potential of these agents has yet to be realized, which could, in part, be because the traditional strategies that are used in clinical trials for anticancer therapies are not appropriate for assessing the efficacy of agents that modulate angiogenesis. Here, we discuss methods for monitoring the biological activity of angiogenic modulators, and innovative approaches to trial design that might facilitate the integration of these agents into anticancer therapy.

L32 ANSWER 11 OF 60 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001609917 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11683633
TITLE: p22 is a novel **plasminogen** fragment with antiangiogenic activity.
AUTHOR: Kwon M; Yoon C S; Fitzpatrick S; Kassam G; Graham K S; Young M K; Waisman D M
CORPORATE SOURCE: Cancer Biology Research Group, Department of Biochemistry & Molecular Biology, University of Calgary, Calgary, Alberta, Canada T2N 4N1.
SOURCE: Biochemistry, (2001 Nov 6) 40 (44) 13246-53.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011102
Last Updated on STN: 20020123
Entered Medline: 20011207
AB Tumor or tumor-associated cells cleave circulating **plasminogen** into three or four **kringle**-containing antiangiogenic fragments, collectively referred to as angiostatin. Angiostatin blocks tumor growth and **metastasis** by preventing the growth of endothelial cells that are critical for tumor vascularization. Here, we show that cancer and normal cells convert **plasminogen** into a novel 22 kDa fragment (p22). Production of this **plasminogen** fragment in a cell-free system has allowed characterization of the structure and activity of the protein. p22 consists of amino acid residues 78-180 of **plasminogen** and therefore embodies the first **plasminogen kringle** (residues 84-162) as well as additional N- and C-terminal residues. Circular dichroism and intrinsic fluorescence spectrum analysis have defined structural differences between p22 and recombinant **plasminogen kringle** 1 (rK1), therefore suggesting a unique conformation for **kringle** 1 within p22. Proliferation of capillary endothelial cells but not cells of other lineages was selectively inhibited by p22 in vitro. In addition, p22 prevented vascular growth of chick chorioallantoic membranes (CAMs) in vivo. Furthermore, administration of p22 at low dose suppressed the growth of murine Lewis **lung** carcinoma (LLC) **metastatic** foci in vivo. This is the first identification of a single **kringle** -containing antiangiogenic **plasminogen** fragment produced under physiological conditions.

L32 ANSWER 12 OF 60 MEDLINE on STN
ACCESSION NUMBER: 2001678017 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11724284
TITLE: Inhibition of tumor growth by **plasminogen**-related protein-B.
AUTHOR: Lewis V O; O'Reilly M S; Gehrmann M; Llinas M; Schaller J; Weissbach L
CORPORATE SOURCE: Orthopaedic Research Laboratories, Massachusetts General Hospital and Harvard Medical School, Boston 02114, USA.. volewis@mail.mdanderson.org
CONTRACT NUMBER: HL-29409 (NHLBI)
SOURCE: Anticancer research, (2001 Jul-Aug) 21 (4A) 2287-91. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011129
Last Updated on STN: 20020123
Entered Medline: 20011207

AB BACKGROUND: Various fragments of the fibrinolytic protein **plasminogen** can act as antiangiogenic factors and inhibit the growth of primary and **metastatic** tumors in mice. **Plasminogen**-related gene-B encodes a putative 9 kDa protein virtually identical to the **plasminogen N-terminal** activation peptide, a 77-amino acid motif that is liberated from the parent **plasminogen** molecule during conversion to the serine proteinase plasmin. Previous data have documented enhanced transcription of **plasminogen**-related gene-B in neoplastic tissues. MATERIALS AND METHODS: We have tested the effects of recombinant versions of **plasminogen**-related protein-B and the **plasminogen N-terminal** activation peptide on the growth of tumors in mice, employing murine tumor cell lines implanted subcutaneously. RESULTS: The recombinant **plasminogen**-related protein-B significantly inhibited the growth of primary tumors in mice, while recombinant **plasminogen N-terminal** activation peptide elicited only a slight inhibition of tumor growth. CONCLUSION: These data suggest that **plasminogen**-related protein-B may have utility as a novel cancer therapeutic.

L32 ANSWER 13 OF 60 EMBASE on STN
ACCESSION NUMBER: 2001244715 EMBASE
TITLE: Patent focus on cancer chemotherapeutics. III Angiogenesis agents: October 2000 - March 2001.
AUTHOR: Connell R.D.; Beebe J.S.
CORPORATE SOURCE: R.D. Connell, Cancer Drug Discovery, Pfizer Global R and D, Eastern Point Road, Groton, CT 06340, United States
SOURCE: Expert Opinion on Therapeutic Patents, (2001) 11/7 (1171-1203).
Refs: 67
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Angiogenesis refers to the formation of new blood vessels from existing blood vessels, a process that is believed to be a key requirement for tumour growth and **metastasis.** Angiogenesis inhibition represents a new approach to cancer chemotherapy and several agents and approaches are now entering late clinical development. This review summarises the key aspects of recent patent applications referring to cancer chemotherapy and cancer drug discovery that involve inhibition or reduction of angiogenesis. The review covers the main mechanism-based approaches such as MMPIs, inhibitors of the growth factor signalling pathways, integrin antagonists and urokinase inhibitors. Additional sections relating to vascular damaging agents, endogenous inhibitors and selected natural products are also included. The scope includes applications that published from October 2000 through March 2001.

L32 ANSWER 14 OF 60 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001537628 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11558062
TITLE: [Tumor cell embolism to pulmonary arteries]. Tumorzellembolien bei **Metastasenleber.**
AUTHOR: Scheppach W; Krenn V; Eck M; Menzel T; Burrows G; Langenfeld H
CORPORATE SOURCE: Medizinische Klinik und, Institut fur Pathologie der Charite, Berlin, Germany.. w.scheppach@medizin.uni-wuerzburg.de
SOURCE: Zeitschrift fur Gastroenterologie, (2001 Aug) 39 (8) 583-6. Journal code: 0033370. ISSN: 0044-2771.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (CASE REPORTS) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20020122
Entered Medline: 20011205

AB A 69-year-old male presented with symptoms of fulminant **lung** embolism and, despite immediate therapy with **plasminogen** activator, died of acute right heart failure. At autopsy multiple tumor cell emboli were detected in small pulmonary vessels in addition to widespread liver **metastases** from an urothelial carcinoma. - In a 23-year-old female a malignant gastric ulcer and multiple liver **metastases** were diagnosed at initial presentation. She too died from pulmonary hypertension due to a series of **lung** embolisms which occurred despite **heparin** therapy. At autopsy, many small pulmonary arteries were filled with adenocarcinoma cells; the primary gastric tumor and liver **metastases** were confirmed.These cases demonstrate that the shedding of tumor cells from hepatic **metastases** can obstruct the pulmonary vessels and lead to acute cor pulmonale. Tumor cell emboli should be considered in the differential diagnosis of acute pulmonary hypertension, especially in patients with a known tumor. They may, however, also represent the first clinical signs of previously unrecognized malignancy.

L32 ANSWER 15 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000318494 EMBASE
TITLE: Cancer treatment with inhibitors of urokinase-type **plasminogen** activator and plasmin.
AUTHOR: Dunbar S.D.; Ornstein D.L.; Zacharski L.R.

CORPORATE SOURCE: L.R. Zacharski, Section of Haematology/Oncology, Department of Medicine, Dartmouth Medical School, 1 Medical Center Drive, Lebanon, NH 03756, United States
SOURCE: Expert Opinion on Investigational Drugs, (2000) 9/9 (2085-2092).
Refs: 70
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The urokinase-type **plasminogen** activator-plasmin system plays an important role in many normal physiological processes including clot lysis, wound healing, embryogenesis and tissue remodelling. It is also involved in the pathogenesis of human malignancy through its ability to mediate tumour cell growth, invasion and **metastatic** dissemination. Interfering with this system is an appealing approach for experimental therapy of malignancy for several reasons. This concept is supported by a wealth of preclinical data. Evidence exists suggesting a role for this system in several major human tumour types. Preliminary evidence suggests that agents which block this pathway are effective in therapeutic doses that are already defined and relatively non-toxic. This form of treatment is not likely to carry cross-resistance with other types of cancer therapy and should be applicable to both localised and advanced tumours. Since heterogeneity in responsiveness among various tumour types is expected, clinical effects in given tumours would provide a basis for interpreting mechanisms of tumour progression in vivo and for future development of drugs with improved efficacy. Inhibition of the urokinase-type **plasminogen** activator-plasmin system remains a promising, but largely untested, area of experimental cancer therapeutics.

L32 ANSWER 16 OF 60 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000269614 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10811477
TITLE: A novel strategy for the tumor angiogenesis-targeted gene therapy: generation of angiostatin from endogenous **plasminogen** by protease gene transfer.
AUTHOR: Matsuda K M; Madoiwa S; Hasumi Y; Kanazawa T; Saga Y; Kume A; Mano H; Ozawa K; Matsuda M
CORPORATE SOURCE: Division of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical School, Tochigi-Ken, Japan.
SOURCE: Cancer gene therapy, (2000 Apr) 7 (4) 589-96.
Journal code: 9432230. ISSN: 0929-1903.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000725

AB When NIH 3T3 fibroblasts were transduced with a retroviral vector containing a cDNA for porcine pancreatic **elastase** 1 and cultured in the presence of affinity-purified human **plasminogen**, the exogenously added **plasminogen** was digested to generate the **kringle** 1-3 segment known as angiostatin, a potent angiogenesis

inhibitor. This was evidenced by immunoblot analysis of the **plasminogen** digests using a monoclonal antibody specifically reacting with the **kringle** 1-3 segment, and by efficient inhibition of proliferation of human umbilical vein endothelial cells by the **plasminogen** digests **isolated** from the culture medium of 3T3 fibroblasts. However, when Lewis **lung** carcinoma cells were transduced with the same vector and injected subcutaneously into mice in their back or via the tail vein, their growth at the injection sites or in the **lungs** was markedly suppressed compared with the growth of similarly treated nontransduced Lewis **lung** carcinoma cells. Nevertheless, the transduced cells were able to grow as avidly as the control cells in vitro. Assuming that the **elastase** 1 secreted from the transduced cells is likely to be exempt from rapid inhibition by its physiological inhibitor, alpha1-protease inhibitor, as shown in the inflammatory tissues, the **elastase** 1 secreted from the tumor cells may effectively digest the **plasminogen** that is abundantly present in the extravascular spaces and generate the **kringle** 1-3 segment in the vicinity of implanted tumor cell clusters. Although the selection of more profitable virus vectors and cells to be transduced awaits further studies, such a protease gene transfer strategy may provide us with a new approach to anti-angiogenesis gene therapy for malignant tumors and their **metastasis** in vivo.

L32 ANSWER 17 OF 60 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000469154 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10970827
TITLE: Profiling the downstream genes of tumor suppressor PTEN in **lung** cancer cells by complementary DNA microarray.
COMMENT: Comment in: Am J Respir Cell Mol Biol. 2000 Sep;23(3):265-9. PubMed ID: 10970813
AUTHOR: Hong T M; Yang P C; Peck K; Chen J J; Yang S C; Chen Y C; Wu C W
CORPORATE SOURCE: Institute of Biomedical Sciences, Academia Sinica, National Health Research Institute, Graduate Institute of Molecular Biology, College of Medicine, National Taiwan University, Taipei.
SOURCE: American journal of respiratory cell and molecular biology, (2000 Sep) 23 (3) 355-63.
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20020823
Entered Medline: 20000929

AB The phosphatase and tensin homology deleted on chromosome 10 (PTEN) is a tumor suppressor gene with sequence homology to tyrosine phosphatases and the cytoskeletal proteins tensin and auxilin. PTEN has recently been shown to inhibit cell migration and the spreading and formation of focal adhesions. This study investigated the role of PTEN in carcinoma invasion in a **lung**-cancer cell line and examined the downstream genes regulated by PTEN. We have previously established a cell-line model in human **lung** adenocarcinoma with different invasive abilities and **metastatic** potentials. Examining PTEN gene expression in these cell lines, we found that a homozygous deletion in exon 5 is associated with high invasive ability. We then constructed stable constitutive and inducible wild-type PTEN-overexpressed transfectants in the highly invasive cell line CL(1-5). We found that an overexpression of PTEN can

inhibit invasion in **lung** cancer cells. To further explore the downstream genes regulated by PTEN, a high-density complementary DNA (cDNA) microarray technique was used to profile gene changes after PTEN overexpression. Our results indicate a panel of genes that can be modulated by PTEN. PTEN overexpression downregulated genes, including integrin alpha(6), laminin beta(3), **heparin-binding** epidermal growth factor-like growth factor, urokinase-type **plasminogen** activator, myb protein B, Akt2, and some expressed sequence tag (EST) clones. In contrast, PTEN overexpression upregulated protein phosphatase 2A1B, ubiquitin protease (unph), secreted phosphoprotein 1, leukocyte **elastase** inhibitor, nuclear factor-kappaB, cyclic adenosine monophosphate response element **binding** protein, DNA ligase 1, heat shock protein 90, and some EST genes. Northern hybridization and flow cytometry analysis also confirmed that PTEN overexpression results in the reduced expression of the integrin alpha(6) subunit. The results of this study indicate that PTEN overexpression may inhibit **lung** cancer invasion by downregulation of a panel of genes including integrin alpha(6). The cDNA microarray technique may be an effective tool to study the downstream function of a tumor suppressor gene.

L32 ANSWER 18 OF 60 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:15606 BIOSIS
DOCUMENT NUMBER: PREV200100015606
TITLE: Successful thrombolysis for **heparin** induced thrombocytopenia and thrombosis after hepatic resection.
AUTHOR(S): Bondoc, A. Y. [Reprint author]; Kapoor, M. [Reprint author]
CORPORATE SOURCE: Memorial Sloan Kettering Cancer Center, NY, NY, USA
SOURCE: Chest, (October, 2000) Vol. 118, No. 4 Suppl., pp. 291S-292S. print.
Meeting Info.: Chest 2000. San Francisco, California, USA. October 22-26, 2000.
CODEN: CHETBF. ISSN: 0012-3692.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Dec 2000
Last Updated on STN: 27 Dec 2000

L32 ANSWER 19 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001129188 EMBASE
TITLE: Hemostatic factors in tumor biology.
AUTHOR: Palumbo J.S.; Degen J.L.
CORPORATE SOURCE: Dr. J.S. Palumbo, Division of Hematology/Oncology, Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-4679, United States
SOURCE: Journal of Pediatric Hematology/Oncology, (2000) 22/3 (281-287).
Refs: 92
ISSN: 1077-4114 CODEN: JPHOFG
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English

L32 ANSWER 20 OF 60 MEDLINE on STN DUPLICATE 8

ACCESSION NUMBER: 2000269974 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10807968
TITLE: Effect of hyperthermia on the viability and the fibrinolytic potential of human cancer cell lines.
AUTHOR: Fukao H; Ikeda M; Ichikawa T; Inufusa H; Okada K; Ueshima S; Matsuo O
CORPORATE SOURCE: Department of Physiology, Kinki University School of Medicine, 377-2 Ohnohigashi, Osakasayama City, Osaka, Japan.. fukao@med.kindai.ac.jp
SOURCE: Clinica chimica acta; international journal of clinical chemistry, (2000 Jun) 296 (1-2) 17-33.
Journal code: 1302422. ISSN: 0009-8981.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000714

AB The effects of heat treatment on the viability and fibrinolytic potential of four cultured human carcinoma cell lines, fibrosarcoma cells (HT-1080), **lung** adenocarcinoma cells with highly **metastatic** potential (HAL-8), melanoma cells (Bowes) and osteosarcoma cells (NY), determined by measuring their levels of urokinase-type **plasminogen** activator (u-PA) and its specific receptor (u-PAR), were investigated by comparing them with those of human umbilical vein endothelial cells (HUVECs). HUVECs **incubated** at 43 degrees C for 120 min exhibited no decrease in viability but exhibited an increase in both u-PA and u-PAR. HT-1080 and HAL-8 showed a moderately high heat-resistance (viability, 60-90%) that correlated with the reduction of u-PAR but not u-PA. On the other hand, Bowes and NY cells, with poor heat-resistance (viability, 20-50%), exhibited stronger cell-associated u-PA activity when they survived at 43 degrees C for 120 min. Since the u-PA/u-PAR system is directly involved in the invasiveness and **metastatic** potential of carcinoma cells, hyperthermia would alter the biological activity of these carcinoma cells.

L32 ANSWER 21 OF 60 MEDLINE on STN
ACCESSION NUMBER: 1999240722 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10224095
TITLE: Systemic gene delivery expands the repertoire of effective antiangiogenic agents.
AUTHOR: Liu Y; Thor A; Shtivelman E; Cao Y; Tu G; Heath T D; Debs R J
CORPORATE SOURCE: Geraldine Brush Cancer Research Institute at the California Pacific Medical Center, San Francisco, California 94115, USA.
CONTRACT NUMBER: CA58207 (NCI)
CA58914 (NCI)
CA71422 (NCI)
SOURCE: Journal of biological chemistry, (1999 May 7) 274 (19) 13338-44.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614

Last Updated on STN: 19990614
Entered Medline: 19990603

AB **Cationic** liposome-DNA complex (CLDC)-based intravenous gene delivery targets gene expression to vascular endothelial cells, macrophages and tumor cells. We used systemic gene delivery to **identify** anti-angiogenic gene products effective against **metastatic** spread in tumor-bearing mice. Specifically, CLDC-based intravenous delivery of the p53 and GM-CSF genes were each as effective as the potent antiangiogenic gene, angiostatin, in reducing both tumor **metastasis** and tumor angiogenesis. Combined delivery of these genes did not increase anti-tumor activity, further suggesting that each gene appeared to produce its **antimetastatic** activity through a common antiangiogenic pathway. CLDC-based intravenous delivery of the human wild type p53 gene transfected up to 80% of tumor cells **metastatic** to **lung.** Furthermore, it specifically induced the expression of the potent antiangiogenic gene, thrombospondin-1, indicating that p53 gene delivery in vivo may inhibit angiogenesis by inducing endogenous thrombospondin-1 expression. CLDC-based delivery also identified a novel anti-tumor activity for the **metastasis** suppressor gene CC3. Thus, CLDC-based intravenous gene delivery can produce systemic antiangiogenic gene therapy using a variety of different genes and may be used to assess potential synergy of combined anti-tumor gene delivery and to **identify** novel activities for existing anti-tumor genes.

L32 ANSWER 22 OF 60 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2000047523 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10582698
TITLE: Inhibition of tumor growth correlates with the expression level of a human angiostatin transgene in transfected B16F10 melanoma cells.
AUTHOR: Ambs S; Dennis S; Fairman J; Wright M; Papkoff J
CORPORATE SOURCE: Valentis Inc., Burlingame, California 94010, USA.
SOURCE: Cancer research, (1999 Nov 15) 59 (22) 5773-7.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991214

AB Although the therapeutic value of angiostatin, a proteolytic fragment of **plasminogen**, has been recognized for the treatment of cancer, the production of bioactive angiostatin remains a difficult task. Here we report that expression of a cDNA encoding a secreted, four-**kringle** human angiostatin inhibited tumor growth of B16F10 melanoma cells in mice but did not suppress tumor cell growth in culture. After transfection and selection, stable expression of the angiostatin cDNA was demonstrated in several B16F10 clones by quantitative mRNA analysis using the Taqman method. Cells that expressed angiostatin at either a low, medium, or high level were injected into C57BL/6 mice. s.c. Growth of B16F10 tumors was diminished by the angiostatin transgene, and the inhibition was directly proportional to the expression level of angiostatin in the transfected cells. However, suppression of s.c. tumor growth was transient, and eventually, tumors emerged with a strongly decreased expression of the transgene. Angiostatin expression also reduced **lung metastasis** from i.v.-injected B16F10 cells. Our data indicate that a cDNA encoding bioactive human angiostatin is potentially useful for

gene therapy of human cancers, but the delivery of the transgene may require repeated dosing to achieve sustained dormancy of primary tumors and cancer **metastases.**

L32 ANSWER 23 OF 60 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000393808 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10919717
TITLE: Soluble fibrin augments platelet/tumor cell adherence in vitro and in vivo, and enhances experimental **metastasis.**
AUTHOR: Biggerstaff J P; Seth N; Amirkhosravi A; Amaya M; Fogarty S; Meyer T V; Siddiqui F; Francis J L
CORPORATE SOURCE: Research and Clinical Laboratories, Walt Disney Memorial Cancer Institute at Florida Hospital, Orlando 32804, USA.. John_Biggerstaff@mail.fhmis.net
SOURCE: Clinical & experimental metastasis, (1999) 17 (8) 723-30. Journal code: 8409970. ISSN: 0262-0898.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000817

AB There is considerable evidence for a relationship between hemostasis and malignancy. Since platelet adhesion to tumor cells has been implicated in the **metastatic** process and plasma levels of fibrinogen (Fg) and soluble fibrin (sFn) monomer are increased in cancer, we hypothesized that these molecules might enhance tumor-platelet interaction. We therefore studied **binding** of sFn monomer to tumor cells in a static microplate adhesion assay and determined the effect of pre-treating tumor cells with sFn on tumor cell-induced thrombocytopenia and experimental **metastasis.** Soluble fibrin (produced by adding thrombin to FXIII- and **plasminogen**-free Fg in the presence of Gly-Pro-Arg-Pro-amide (GPRP-NH2) significantly increased platelet adherence to tumor cells. This effect was primarily mediated by the integrins alphaIIb beta3 on the platelet and CD 54 (ICAM-1) on the tumor cells. Platelets adhered to untreated A375 cells (28 +/- 8 platelets/tumor cell) and this was not significantly affected by pre-treatment of the tumor cells with fibrinogen or GPRP-NH2. Although thrombin treatment increased adherence, pre-**incubation** of the tumor cells with sFn resulted in a further increase in platelet **binding** to tumor cells. In contrast to untreated tumor cells, intravenous injection of sFn-treated A 375 cells reduced the platelet count in anticoagulated mice, supporting the in vitro finding that sFn enhanced tumor cell-platelet adherence. In a more aggressive model of experimental **metastasis**, treating tumor cells with sFn enhanced **lung** seeding by 65% compared to untreated cells. Extrapolation of our data to the clinical situation suggests that coagulation activation, and subsequent increase in circulating Fn monomer, may enhance platelet adhesion to circulating tumor cells and thereby facilitate **metastatic** spread.

L32 ANSWER 24 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999036528 EMBASE
TITLE: Hypoxia-mediated stimulation of carcinoma cell invasiveness via upregulation of urokinase receptor expression.
AUTHOR: Graham C.H.; Forsdike J.; Fitzgerald C.J.; Macdonald-Goodfellow S.

CORPORATE SOURCE: C.H. Graham, Dept. of Anatomy and Cell Biology, Botterell Hall, Queen's University, Kingston, Ont. K7L 3N6, Canada. grahamc@post.queensu.ca
SOURCE: International Journal of Cancer, (4 Feb 1999) 80/4 (617-623).
Refs: 27
ISSN: 0020-7136 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Tumor hypoxia and high levels of expression of the urokinase-type **plasminogen** activator (uPA) receptor (uPAR) represent a poor clinical outcome for patients with various cancers. Here, we examined the effect of hypoxia on in vitro invasion of extracellular matrix and uPAR expression by human carcinoma cells. Compared with culture under 20% O2, culture for up to 24 hr under 1% or 4% O2 resulted in increased cell surface uPAR. However, the highest uPAR levels were observed in cells cultured under 1% O2. Culture of MDA-MB-231 breast carcinoma cells under hypoxia also resulted in increased uPAR mRNA levels. Furthermore, **incubation** with cobalt chloride or with an iron chelator also resulted in elevated uPAR expression, while presence of 30% carbon monoxide in the hypoxic atmosphere reduced the hypoxia-mediated uPAR mRNA upregulation. Increased uPAR expression was paralleled by higher cell-associated uPA levels and lower levels of secreted uPA as determined by gel zymography performed on cell extracts and culture-conditioned media. In addition, the in vitro invasiveness of MDA-MB231 breast carcinoma cells was significantly higher when the invasion assay was performed under hypoxic conditions. This effect of hypoxia on invasion was abrogated by including in the assay a monoclonal, function-blocking anti-uPAR antibody or by the presence of 30% carbon monoxide in the hypoxic atmosphere. Our findings indicate that hypoxia stimulates carcinoma cell invasiveness by upregulating uPAR expression on the cell surface through a mechanism that requires a putative heine protein. Through a similar mechanism, hypoxia may stimulate tumor invasion and **metastasis** in vivo.

L32 ANSWER 25 OF 60 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2000001943 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10529387
TITLE: The tumor-suppressing activity of angiostatin protein resides within **kringles** 1 to 3.
AUTHOR: MacDonald N J; Murad A C; Fogler W E; Lu Y; Sim B K
CORPORATE SOURCE: EntreMed, Inc., 9640 Medical Center Drive, Rockville, Maryland, 20850, USA.
SOURCE: Biochemical and biophysical research communications, (1999 Oct 22) 264 (2) 469-77.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991207

AB Angiostatin protein, which comprises the first four **kringle** domains of **plasminogen**, is an endogenous inhibitor of angiogenesis that inhibits the growth of experimental primary and **metastatic** tumors. Truncation of Angiostatin K1-4 to K1-3 retained the activity of Angiostatin. We recombinantly expressed full-length human Angiostatin protein corresponding to the first four **kringle** domains of human **plasminogen** and a truncated form of the Angiostatin protein, **kringles** 1-3. Purified recombinant Angiostatin K1-3 and K1-4 proteins inhibited the formation of experimental B16-BL6 **lung metastases** by greater than 80% when administered at 30 nmol/kg/day. We demonstrate for the first time that Angiostatin protein, consisting of the first three **kringle** domains of human **plasminogen**, has in vivo biological activity in this assay indistinguishable from that of the full-length Angiostatin K1-4 protein and that the fourth **kringle** of **plasminogen**, when linked in sequence to K1-3, plays no direct role in the antitumor activity of Angiostatin.

L32 ANSWER 26 OF 60 JAPIO (C) 2004 JPO on STN
ACCESSION NUMBER: 1998-114796 JAPIO
TITLE: PLASMID FRAGMENT HAVING INHIBITORY EFFECT ON TUMOR **METASTASIS** PROLIFERATION AND PREPARATION OF THE SAME
INVENTOR: **MORIKAWA WATARU**; MIYAMOTO SEIJI
PATENT ASSIGNEE(S): CHEMO SERO THERAPEUT RES INST
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 10114796	A	19980506	Heisei	C07K014-745

APPLICATION INFORMATION
STN FORMAT: JP 1996-287651 19961009
ORIGINAL: JP08287651 Heisei
PRIORITY APPLN. INFO.: JP 1996-287651 19961009
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1998
AN 1998-114796 JAPIO
AB PROBLEM TO BE SOLVED: To obtain the subject new protein fragment useful for clinical treat ment for solid cancers such as **lung** cancer and colon cancer, showing **heparin- binding** properties, comprising an **elastase** decomposition product of **lys-plasminogen.**
SOLUTION: This new **plasminogen** fragment comprises an **elastase** decomposition product of **lys-plasminogen** and has inhibitory effects on tumor **metastasis** proliferation and **heparin binding** properties and is useful for clinical treatment for solid cancers represented by **lung** cancer and colon cancer. The **plasminogen** is obtained by directly adding plasmin to a **plasminogen**-containing solution or indirectly and naturally digesting the **plasminogen** by using **tranexamic acid**, etc., to prepare **lys -plasminogen**, then treating the **lys plasminogen** with **elastase**, passing the decomposition product-containing solution through a **carrier** using **heparin** as a ligand and adsorbing and eluting.

L32 ANSWER 27 OF 60 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER: 1999002492 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9788443
TITLE: Cloning and functional characterization of a new phosphatidyl-inositol anchored molecule of a **metastasizing** rat pancreatic tumor.
AUTHOR: Rosel M; Claas C; Seiter S; Herlevsen M; Zoller M
CORPORATE SOURCE: Department of Tumor Progression and Immune Defense, German Cancer Research Center, Heidelberg.
SOURCE: Oncogene, (1998 Oct 15) 17 (15) 1989-2002. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ001043
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981106

AB We have described recently a panel of **metastasis**-associated antigens expressed on a rat pancreatic tumor. One of these molecules, recognized by the monoclonal antibody C4.4 and named accordingly C4.4A, was under physiological conditions expressed only in the gravid uterus and on epithelial of the upper gastrointestinal tract. The cDNA of the antigen has been **isolated** and cloned. The 1,637 b cDNA codes for a 352 amino acid long glycosylphosphatidyl-inositol (GP) anchored molecule, whose molecular weight varies in different cells between 94-98 kD according to the degree of N- and O-**glycosylation.** Data base searches have revealed a low degree of homology to the receptor for the **plasminogen** activator (uPAR). After intrafootpad and intravenous application of C4.4A transfected and mock-transfected tumor cells, an increased number of **lung** nodules was detected with the former, whereby the individual **metastatic** nodules amalgamated without any encapsulation of the tumor tissue. Furthermore, C4.4A is involved in adhesion to laminin and, although transfection of a non-**metastasizing** tumor line with the molecule was not sufficient, constitutively C4.4A-positive tumor cells penetrated through matrigel. This process could be completely prevented by C4.4. Finally, we could demonstrate that uPA, albeit weakly, **bound** to the C4.4A molecule. In view of the observed influence of C4.4A on **metastasis** formation and matrix penetration it is tempting to speculate that this newly described **metastasis**-associated molecule may exert functional activity similar to the uPAR, i.e. via activation of matrix degrading enzymes. By the very restricted expression of the molecule in the adult organism, modulation of C4.4A could well be of therapeutic interest.

L32 ANSWER 28 OF 60 MEDLINE on STN
ACCESSION NUMBER: 1998372766 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9705957
TITLE: Angiostatin-mediated suppression of cancer **metastases** by primary neoplasms engineered to produce granulocyte/macrophage colony-stimulating factor.
AUTHOR: Dong Z; Yoneda J; Kumar R; Fidler I J
CORPORATE SOURCE: Department of Cell Biology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA.. zdong@notes.mdacc.tmc.edu
CONTRACT NUMBER: CA16672 (NCI)
R35-CA-42107 (NCI)
SOURCE: Journal of experimental medicine, (1998 Aug 17) 188 (4)

755-63.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981007

AB We determined whether tumor cells consistently generating granulocyte/macrophage colony- stimulating factor (GM-CSF) can recruit and activate macrophages to generate angiostatin and, hence, inhibit the growth of distant **metastasis.** Two murine melanoma lines, B16-F10 (syngeneic to C57BL/6 mice) and K-1735 (syngeneic to C3H/HeN mice), were engineered to produce GM-CSF. High GM-CSF (>1 ng/10(6) cells)- and low GM-CSF (<10 pg/10(6) cells)-producing clones were identified. Parental, low, and high GM-CSF-producing cells were injected subcutaneously into syngeneic and into nude mice. Parental and low-producing cells produced rapidly growing tumors, whereas the high-producing cells produced slow-growing tumors. Macrophage density inversely correlated with tumorigenicity and directly correlated with steady state levels of macrophage **metalloelastase** (MME) mRNA. B16 and K-1735 subcutaneous (s.c.) tumors producing high levels of GM-CSF significantly suppressed **lung metastasis** of 3LL, UV-2237 fibrosarcoma, K-1735 M2, and B16-F10 cells, but parental or low-producing tumors did not. The level of angiostatin in the serum directly correlated with the production of GM-CSF by the s.c. tumors. Macrophages **incubated** with medium conditioned by GM-CSF-producing B16 or K-1735 cells had higher MME activity and generated fourfold more angiostatin than control counterparts. These data provide direct evidence that GM-CSF released from a primary tumor can upregulate angiostatin production and suppress growth of **metastases.**

L32 ANSWER 29 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 97309495 EMBASE
DOCUMENT NUMBER: 1997309495
TITLE: The mechanism of cancer-mediated conversion of **plasminogen** to the angiogenesis inhibitor angiostatin.
AUTHOR: Gately S.; Twardowski P.; Stack M.S.; Cundiff D.L.; Grella D.; Castellino F.J.; Enghild J.; Kwaan H.C.; Lee F.; Kramer R.A.; Volpert O.; Bouck N.; Soff G.A.
CORPORATE SOURCE: G.A. Soff, Northwestern University, School of Medicine, Searle Building, 320 East Superior State, Chicago, IL 60611, United States. gasoff@merle.acns.nwu.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/20 (10868-10872). Refs: 26
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Angiostatin, a potent naturally occurring inhibitor of angiogenesis and growth of tumor **metastases**, is generated by cancer-mediated proteolysis of **plasminogen.** Human prostate carcinoma cells (PC-3) release enzymatic activity that converts **plasminogen** to

angiostatin. We have now identified two components released by PC-3 cells, urokinase (uPA) and free sulfhydryl donors (FSDs), that are sufficient for angiostatin generation. Furthermore, in a defined cell-free system, **plasminogen** activators [uPA, tissue-type **plasminogen** activator (tPA), or streptokinase], in combination with one of a series of FSDs (N-acetyl-L-cysteine, D-penicillamine, captopril, L-cysteine, or reduced glutathione] generate angiostatin from **plasminogen.** An essential role of plasmin catalytic activity for angiostatin generation was identified by using recombinant mutant **plasminogens** as substrates. The wild-type recombinant **plasminogen** was converted to angiostatin in the setting of uPA/FSD; however, a **plasminogen** activation site mutant and a catalytically inactive mutant failed to generate angiostatin. Cell-free derived angiostatin inhibited angiogenesis in vitro and in vivo and suppressed the growth of Lewis **lung** carcinoma **metastases.** These findings define a direct mechanism for cancer-cell-mediated angiostatin generation and permit large-scale production of bioactive angiostatin for investigation and potential therapeutic application.

L32 ANSWER 30 OF 60 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 97238710 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9102221
TITLE: A recombinant human angiostatin protein inhibits experimental primary and **metastatic** cancer.
AUTHOR: Sim B K; O'Reilly M S; Liang H; Fortier A H; He W; Madsen J W; Lapcevich R; Nacy C A
CORPORATE SOURCE: EntreMed, Inc., Rockville, Maryland 20850, USA.
CONTRACT NUMBER: 1 R43 CA67641-01 (NCI)
SOURCE: Cancer research, (1997 Apr 1) 57 (7) 1329-34.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970424
Last Updated on STN: 19970424
Entered Medline: 19970417

AB Endogenous murine angiostatin, identified as an internal fragment of **plasminogen**, blocks neovascularization and growth of experimental primary and **metastatic** tumors in vivo. A recombinant protein comprising **kringles** 1-4 of human **plasminogen** (amino acids 93-470) expressed in Pichia pastoris had physical properties (molecular size, **binding** to lysine, reactivity with antibody to **kringles** 1-3) that mimicked native angiostatin. This recombinant Angiostatin protein inhibited the proliferation of bovine capillary endothelial cells in vitro. Systemic administration of recombinant Angiostatin protein at doses of 1.5 mg/kg suppressed the growth of Lewis **lung** carcinoma-low **metastatic** phenotype **metastases** in C57BL/6 mice by greater than 90%; administration of the recombinant protein at doses of 100 mg/kg also suppressed the growth of primary Lewis **lung** carcinoma-low **metastatic** phenotype tumors. These findings demonstrate unambiguously that the antiangiogenic and antitumor activity of endogenous angiostatin resides within **kringles** 1-4 of **plasminogen.**

L32 ANSWER 31 OF 60 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 14
ACCESSION NUMBER: 1997:167625 BIOSIS
DOCUMENT NUMBER: PREV199799474228

TITLE: **N-terminal** peptide of type III procollagen: A possible predictor of colorectal carcinoma recurrence.
AUTHOR(S): Plebani, Mario [Reprint author]; Basso, Daniela; Roveroni, Giovanni; De Paoli, Massimo; Galeotti, Fabrizio; Corsini, Augusto
CORPORATE SOURCE: Dep. Med. Lab., Lab. Centrale, Azienda Ospedaliera, Via Giustiniani 2, 35128 Padova, Italy
SOURCE: Cancer, (1997) Vol. 79, No. 7, pp. 1299-1303.
CODEN: CANCAR. ISSN: 0008-543X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Apr 1997
Last Updated on STN: 24 Apr 1997

AB BACKGROUND: The first step of colorectal carcinoma spread depends on the ability of the tumor cells to degrade and invade the extracellular matrix (ECM). The objectives of the current study were to evaluate the serum pattern of laminin, C-terminal peptide of Type I (PIP), and **N-terminal** peptide of Type III (PIIIP) procollagens, markers of ECM synthesis, in the follow-up of patients after resection for colorectal carcinoma and to evaluate their role in predicting local recurrence or **metastases.** METHODS: A total of 32 patients who had undergone resection for colorectal carcinoma were followed for a median period of 24 months (range, 6-36 months). Every 3 months, laminin, PIP, and PIIIP were measured in the sera together with the tumor markers carcinoembryonic antigen (CEA), CA 19-9, and tissue **plasminogen** activator (TPA). Twenty-one patients (Group 1) had no signs of recurrence, whereas the remaining 11 (Group 2) developed hepatic (n = 7) or pulmonary (n = 4) **metastases.** RESULTS: No variations were observed in either group for laminin, CEA, CA 19-9, or TPA, whereas significant increases in PIP and PIIIP were observed in both groups 3 months after surgery. The increase in PIP and PIIIP at the 3-month follow-up was significantly greater in Group 1 than in Group 2. The difference between values at 3 months and basal values enabled a discrimination between Group 1 and Group 2, with a sensitivity of 36% and 91% and a specificity of 71% and 71% for PIP and PIIIP, respectively. CONCLUSIONS: The authors believe PIIIP is useful as an early prognostic indicator of recurrence in the follow-up of patients who have undergone radical resection for colorectal carcinoma.

L32 ANSWER 32 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 96324242 EMBASE
DOCUMENT NUMBER: 1996324242
TITLE: Inhibition of fibrinolysis by a synthetic urokinase inhibitor enhances **lung** colonization of **metastatic** murine mammary tumor cells.
AUTHOR: Alonso D.F.; Bertolesi G.E.; Farias E.F.; Gomez D.E.; Bal De Kier Joffe E.
CORPORATE SOURCE: Department of Science and Technology, Quilmes National University, R. Saez Pena 180,1876 Bernal, Buenos Aires, Argentina
SOURCE: Oncology Reports, (1996) 3/6 (1055-1058).
ISSN: 1021-335X CODEN: OCRPEW
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have investigated the role of coagulation and fibrinolysis during the **metastatic lung** colonization of F3II mouse mammary carcinoma cells. The selective synthetic urokinase inhibitor B623 significantly enhanced **lung** colonization and blocked the **antimetastatic** effect of **heparin** when administered i.p. during the first stages of **metastasis** formation. In B623-treated mice the overall activity of the fibrinolytic system was reduced and circulating urokinase was specifically inhibited by this agent. In vitro studies demonstrated that B623 induces the aggregation of E3II cells in the presence of mouse plasma and facilitates the entrapment of tumor cells in a fibrin gel matrix. Our data suggest that imbalances of fibrin deposition and removal may dramatically influence **metastatic lung** colonization.

L32 ANSWER 33 OF 60 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 970386353 JICST-EPlus
TITLE: Role of Type 1 **Plasminogen** Activator Inhibitor(PAI-1) in **Metastasis** Formation of Human Fibrosarcoma (HT-1080).
AUTHOR: MATSUDA EIZO
CORPORATE SOURCE: Sch. of Med., Kanazawa Univ.
SOURCE: Kanazawa Daigaku Juzen Igakkai Zasshi (Journal of the Juzen Medical Society), (1996) vol. 105, no. 6, pp. 736-744. Journal Code: G0716A (Fig. 6, Tbl. 1, Ref. 27) ISSN: 0022-7226
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New
AB Monoclonal cell lines from human fibrosarcoma (HT-1080) parental cell line were established using the limited dilution method, and were subsequently screened for levels of type 1-**plasminogen** activator inhibitor(PAI-1) antigen. **Metastatic** potentials were evaluated by counting **metastatic** colonies formed on nude mice **lungs** after tumor cell inoculation, and the correlation between PAI-1 levels and **metastatic** potentials was investigated. Each fibrinolytic parameter was measured using an enzyme-linked immunosorbent assay(ELISA). Four monoclonal cell lines exhibiting stable levels of PAI-1 and urokinasetype pasminogen activator(u-PA) were used for the present study. Their tissue factor(TF) activity was evaluated on the cell surface by measuring prothrombin complex formation and chromogenic substrate conversion. mRNA levels of PAI-1 and u-PA were found to be consistent with antigen levels. There was a highly significant difference in **metastatic** potentials as evaluated by counting **metastatic** colonies in nude mice **lungs** at 3 weeks after the tail vein injection of the respective tumor cells. **Metastatic** potentials significantly correlated with PAI-1 and TF levels. A clone with higher **metastatic** potential was not superior to one with lower **metastatic** potential, with regard to adhessiveness to endothelial cells. However, as compared with other clones, the clone with higher **metastatic** potential could stay in the **lung** longer after attachment. Regarding invasive potential into the extracellular matrix subsequent to the tumor cell's lodgement, no significant difference was observed between clones. To dissolve tumor thrombus (which is thought to be essential for the tumor cell's lodgement), nude mice were treated with **heparin** after tumor cell inoculation. No statistical effect was seen in mice inoculated with tumor cells exhibiting low PAI-1 and low TF. (author abst.)

L32 ANSWER 34 OF 60 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 960871839 JICST-EPlus
TITLE: Change of **Plasminogen** Activators and Plassminogen Activator Inhibitor-1 in AOI Cells under Acidic Culture.
AUTHOR: ITO YOKO; MIYATA NOBUKI
NAKATSUGAWA SHIGEKAZU; OGURI TAKASHI
CORPORATE SOURCE: Aichi Med. Univ.
Nagoya Univ., Sch. of Med.
SOURCE: Nippon Rinsho Seiri Gakkai Zasshi (Japanese Journal of Applied Physiology), (1996) vol. 26, no. 5, pp. 311-320.
Journal Code: Y0689A (Fig. 5, Tbl. 2, Ref. 23)
ISSN: 0286-7052
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New

AB The pH within tumor tissue decrease according to the growth of tumor. The cell growth, invasion, **metastasis** and their relation with tumor associated fibrinolysis were examined in AOI cells under acidic condition. Human **lung** cancer AOI cells which had the high **metastatic** ability in vivo were cultured in low pH media (pH7.4, 6.9, 6.4 and 5.9) from 0 day or 4 days (log stage) after seeding, and their cell growth, pH and antigen levels of tPA, uPA and PAI-1 in each medium were measured. The following results were obtained. 1) The growth of AOI cells under pH5.9 culture decreased extremely, but their growth under higher pH culture were the same as the control. 2) The pH of each culture medium decreased on 6 days after culture and increased a little after that. 3) Although, tPA was hardly produced by AOI cells under pH5.9 culture from 0 day after seeding, tPA in other pH group did not change from the control. Under pH5.9 culture from log stage of growth, tPA production increased on 9 days after culture. 4) Although, uPA production by AOI cells decreased under pH5.9 culture from 0 day after seeding, there was no change under other pH in comparison with control. uPA production was delayed according to the decrease of pH in medium from log stage and the amount of uPA antigen in pH5.9 culture was the highest amount in all groups. 5) PAI-1 production ofAOI cells had decreased a little under pH5.9 culture compared to other pH. Under pH7.4 and 6.9 culture, PAI-1 increased transiently on 6 days after culture which agreed with the peak of uPA production in control. These results suggested that the decrease of pH in log stage of AOI cells growth stimulate the production of uPA, and the uPA might advance to **metastasis** and invasion of AOI cells in vivo. (author abst.)

L32 ANSWER 35 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95129617 EMBASE
DOCUMENT NUMBER: 1995129617
TITLE: Blood coagulation activation in cancer: Challenges for cancer treatment.
AUTHOR: Zacharski L.R.; Costantini V.
CORPORATE SOURCE: VA Medical Center,White River Junction, VT 05009-0001, United States
SOURCE: Hamostaseologie, (1995) 15/1 (14-20).
ISSN: 0720-9355 CODEN: HAEMD2
COUNTRY: Germany
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English; German
AB It has been known for over a century that blood coagulation and fibrinolysis pathways are activated systemically in patients with malignancy. Recent studies have revealed evidence for two distinct pathways of interaction between tumor cells and the host coagulation mechanism that include production of either initiators of thrombin formation or expression of **plasminogen** activators by the tumor cells in situ within intact tumor tissue. Studies in specific in vitro and animal models of malignancy have implicated either tumor cell procoagulants or urokinase in mechanisms of tumor cell proliferation, invasion, and **metastasis.** We have formulated a classification of human tumor types based on detection of components of either of these pathways in situ. Type I tumors are those in which the tumor cells are associated with an intact coagulation pathway that leads to thrombin formation at the tumor periphery but in which the tumor cells lack urokinase. Type II tumors are those in which the tumor cells express urokinase but lack an associated coagulation pathway leading to thrombin formation. Type III tumors are those that express neither of these pathways, or exhibit some other pattern of interaction. Evidence suggests that anticoagulant therapy is capable of ameliorating the clinical course of a procoagulant tumor type namely, small cell carcinoma of the **lung.** This approach may be effective in other type I tumors. Clinical trials of agents capable of inhibiting urokinase-initiated proteolysis are required to clarify cause/effect relationships in urokinase-expressing tumors. Exploration of the coagulation-cancer interaction holds considerable promise for imaginative new approaches to cancer treatment that are not only relatively nontoxic and low cost, but also effective because they may interrupt fundamental mechanisms of malignant growth control.

L32 ANSWER 36 OF 60 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 940990807 JICST-EPlus
TITLE: Inhibitory Effect of Oversulfated Fucoidan on Invasion through Reconstituted Basement Membrane by Murine Lewis **Lung** Carcinoma.
AUTHOR: SOEDA S; ISHIDA S; SHIMENO H; NAGAMATSU A
CORPORATE SOURCE: Fukuoka Univ., Fukuoka
SOURCE: Jpn J Cancer Res, (1994) vol. 85, no. 11, pp. 1144-1150. Journal Code: F0633A (Fig. 7, Ref. 23)
ISSN: 0910-5050
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New
AB We investigated the effects of native, oversulfated, and desulfated fucoidans and **heparin** on the invasion of 3 LL cells through Matrigel. Of the four polysaccharides tested, oversulfated fucoidan was the most potent inhibitor of tumor cell invasion and inhibited most potently and specifically the tumor cell adhesion to laminin. Sodium dodecyl sulfate-polyacrylamide gel electrophoretic analysis of the **binding** of **elastase**-cleaved laminin to fucoidan- and **heparin**-Sepharoses showed that both polysaccharides **bound** to the 62 and 56 kDa fragments. Pretreatment of 3LL cells with native or oversulfated fucoidan reduced their adhesive potency to laminin. The two fucoidans inhibited further the laminin **binding** of 3 LL cells which had been pretreated with a laminin-based pentapeptide, YIGSR. These results suggest that fucoidan specifically **binds** to not only the **heparin binding** domain(s) of laminin but also site(s) other than the cell surface laminin receptor. 3 LL cells secreted a 50 kDa

form of urokinase-type **plasminogen** activator (u-PA). The extracellular level of u-PA activity was increased 1.7 times by addition of laminin but not type IV collagen. Oversulfated fucoidan most potently reduced the increased u-PA levels. Therefore, the reduction in in vitro invasiveness of 3 LL cells in response to either fucoidan or its oversulfated derivative may result from an inhibition of physical interaction between the tumor cells and the Matrigel (laminin), followed by a suppression of the laminin-induced increase in extracellular u-PA. (author abst.)

L32 ANSWER 37 OF 60 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 94252721 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8194882
TITLE: Inhibition of **metastasis** of Lewis **lung** carcinoma by a synthetic peptide within growth factor-like domain of urokinase in the experimental and spontaneous **metastasis** model.
AUTHOR: Kobayashi H; Gotoh J; Fujie M; Shinohara H; Moniwa N; Terao T
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Shizuoka, Japan.
SOURCE: International journal of cancer. Journal international du cancer, (1994 Jun 1) 57 (5) 727-33.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940707
Last Updated on STN: 20000303
Entered Medline: 19940627

AB Four synthetic peptides (residues 20-30 and 17-34) within the growth factor-like domain (GFD) of murine and human urokinase-type **plasminogen** activator (uPA) were examined to determine whether they inhibit production of experimental and spontaneous **lung** **metastasis** by murine Lewis **lung** carcinoma (3LL) cells. In an in vivo experimental **metastasis** assay, which determines mainly the later steps of the **metastatic** migration process (extravasation from the bloodstream and then growth into pulmonary tumor), none of the peptides introduced by i.v. single co-injection into syngeneic C57B1/6 mice inhibited pulmonary **metastasis**, when 3LL cells were pre-**incubated** with the peptides followed by i.v. co-injection of the peptide and cells. In addition, none of the peptides, when injected i.p. daily for 7 days after i.v. tumor cell inoculation, reduced the number of **lung** tumor colonies. In a second in vivo assay that measures **metastasis** from a primary tumor (spontaneous **metastasis** model), multiple i.p. injections of the mouse peptide 17-34 for 7 days after s.c. tumor cell inoculation significantly inhibited **metastatic** **lung** tumor colonization in a dose-dependent manner, whereas human peptide 17-34 had no effect. Mouse and human peptide 20-30 had no effect either. The inhibition of **lung** **metastasis** was not due to direct antitumor effects of mouse peptide 17-34. Our results indicate that occupation of uPA receptors on 3LL cells by the enzymatically inactive mouse peptide 17-34 or prevention of **rebinding** of uPA synthesized by tumor cells to their receptor specifically reduced tumor cell invasion and formation of **metastasis** and that uPA may regulate more efficiently the mechanism involved in the entry of tumor cells into vascular circulation than extravasation during the **metastatic** process.

L32 ANSWER 38 OF 60 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 940359081 JICST-EPlus
TITLE: A case of pulmonary embolism following total prostatectomy.
AUTHOR: NISHINO YOSHINORI; FUJIHIRO SHIGERU
CORPORATE SOURCE: Gifu Red Cross Hospital
SOURCE: Hinyokika Kiyo (Acta Urologica Japonica), (1994) vol. 40, no. 3, pp. 253-256. Journal Code: F0649A (Fig. 3, Tbl. 1, Ref. 11)
CODEN: HIKYAJ; ISSN: 0018-1994
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Short Communication
LANGUAGE: Japanese
STATUS: New
AB A 73-year-old man presented to our hospital complaining of dysuria and nocturia. The examination revealed prostatic cancer. **Metastatic** cancer was not revealed by the examination. He underwent total prostaectomy and iliac lymphoadenectomy. Pathological examination of the surgical specimen revealed moderately differentiated adenocarcinoma of the prostate with right iliac lymph node **metastasis.** On the 33rd postoperative day, he suddenly developed chest pain, dyspnea, tachycardia, and tachypnea. Arterial Po2 was 62mmHg, and chest X-ray showed right ventricular hypertrophy. Pulmonary perfusion scan revealed multiple cold areas throughout both **lung** fields. The diagnosis was pulmonary embolism and anti-coagulant therapy was immediately successful in resolving his symptoms. We suggest that pulmonary embolism should be considered as one of the postoperative complications of urological operations. (author abst.)

L32 ANSWER 39 OF 60 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1994:523749 BIOSIS
DOCUMENT NUMBER: PREV199497536749
TITLE: Effect of anticoagulation and inhibition of PAI-1 activity on initial pulmonary arrest and **lung** **metastasis** formation in a nude mouse model with selected clones of human fibrosarcoma HT-1080 cells.
AUTHOR(S): Matsuda, E. [Reprint author]; Tsuchiya, H.; Hufnagl, P. [Reprint author]; Zheng, X. [Reprint author]; Wojta, J. [Reprint author]; Binder, B. R.
CORPORATE SOURCE: Lab. Clin. Exp. Physiol., Univ. Vienna, Vienna, Austria
SOURCE: Fibrinolysis, (1994) Vol. 8, No. SUPPL. 1, pp. 7. Meeting Info.: XIIth International Congress on Fibrinolysis. Leuven, Belgium. September 18-22, 1994. CODEN: FBRIE7. ISSN: 0268-9499.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 1994
Last Updated on STN: 3 Dec 1994

L32 ANSWER 40 OF 60 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1993:390213 BIOSIS
DOCUMENT NUMBER: PREV199396065513
TITLE: Immunohistochemical study of tumor cell-associated **plasminogen** activators and **plasminogen** activator inhibitors in **lung** carcinomas.
AUTHOR(S): Gris, Jean-Christophe [Reprint author]; Schved, Jean-Francois; Marty-Double, Christiane; Mauboussin,

Jean-Marc; Balmes, Pierre
CORPORATE SOURCE: Lab. Hematologie, CHU, 5 rue Hoche, BP 26, Nines Cedex F-30006, France
SOURCE: Chest, (1993) Vol. 104, No. 1, pp. 8-13.
CODEN: CHETBF. ISSN: 0012-3692.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Aug 1993
Last Updated on STN: 23 Aug 1993

AB Study objective: To compare the expression of **plasminogen** activators (PA) and **plasminogen** activator inhibitors (PAI) in normal **lung** mucosa and **lung** carcinomas. Design: Immunohistochemical localization of urokinase-type PA (uPA), tissue-type PA (tPA), type 1 PAI (PAI-1), and type 2 PAI (PAI-2) in four normal **lung** biopsy specimens and in four adenocarcinomas (AC), four squamous carcinomas (SC), two large-cell carcinomas (LCC), and ten small-cell carcinomas (SCC) biopsy specimens. Qualitative immunostaining scoring system. Results: tPA and uPA immunostaining scores from all specimens were statistically similar. The cellular staining for uPA and tPA was generally constant (normal epithelial layers, AC cells, SC cells) except for LCC cells (inconstant uPA staining, p lt 10-3). Both PAIs were detected in cells of the normal epithelial layer. The four carcinoma cell types stained for PAI in a statistically different pattern (p lt 10-3). Cells of the peripheral cords of SCC were inconstantly PAI-1 and PAI-2 positive (p lt 10-3). LCC were PAI-2 negative and inconstantly stained for PAI-1. SCC cells were PAI-1 and PAI-2 negative. Conclusion: **Lung** carcinomas of worst clinical prognosis no longer express PAI reactivity. The imbalance of the **plasminogen** activation pathway may favor the spreading of the more invasive histologic types of bronchogenic carcinomas.

L32 ANSWER 41 OF 60 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 92365345 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1354271
TITLE: Tetranectin, a **plasminogen kringle** 4-**binding** protein. Cloning and gene expression pattern in human colon cancer.
COMMENT: Comment in: Lab Invest. 1993 Mar;68(3):367-8. PubMed ID: 8450653
AUTHOR: Wewer U M; Albrechtsen R
CORPORATE SOURCE: Laboratory of Molecular Pathology, University Institute of Pathological Anatomy, Copenhagen, Denmark.
SOURCE: Laboratory investigation; a journal of technical methods and pathology, (1992 Aug) 67 (2) 253-62.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X64559
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920925
Last Updated on STN: 19950206
Entered Medline: 19920916

AB BACKGROUND: Tetranectin is a recently discovered protein that **binds** to **kringle** 4 region of **plasminogen** (Clemmensen I, Petersen LC, Kluft C. Eur J Biochem 1986; 156:327. EXPERIMENTAL DESIGN: The mRNA encoding human tetranectin was cloned by using degenerate primers in a reverse transcriptase reaction followed by polymerase chain reaction amplification. The resulting polymerase chain

reaction product was examined by DNA sequencing and subsequently used as probe for screening a human placental cDNA library. A full length cDNA clone (TET-1) was **isolated**, characterized, and used for Northern blot and in situ hybridization. RESULTS: DNA sequencing analysis revealed a 874-base pair cDNA containing an open reading frame of 606 base pairs encoding 202 amino acids. A classical signal peptide was present starting with the initiation methionine. The mature tetranectin chain consisted of 181 amino acids (M(r) = 20,169). The 3' noncoding region contained a single polyadenylation signal and a 26-residue poly A tail. The predicted amino acid sequence of the mature tetranectin chain showed, except for one amino acid, complete identity to that obtained by sequencing of the native protein (Fuhlendorff J, Clemmensen I, Magnusson S, Biochemistry 1987;26:6757). Northern blot of poly A+ revealed a single band of approximately 1 kb. Northern blot analysis of poly A+ **isolated** from a series of normal human tissues (**lung**, liver, spleen, kidney, and pancreas) revealed a distinct hybridization band that was especially prominent in the **lungs** and spleen. No hybridization signal was detected in three carcinoma cell lines examined in parallel. Northern blot analysis of poly A+ RNA **isolated** from solid tumors revealed a tetranectin specific mRNA band. In situ hybridizations on tissue sections of colon carcinomas and normal colon tissues revealed a strong and distinct hybridization signal of stromal cells in colon carcinomas but not in tumor cells. Only a few stromal cells were labeled in the normal colon. Immunohistochemically, tetranectin was found in a fibrillar-like pattern in the extracellular matrix around the tumor islands and was not detectable in the normal colon stromal tissue. **Plasminogen** exhibited a similar immunohistochemical staining pattern as tetranectin. CONCLUSIONS: Human tetranectin cDNA comprises 874 base pairs including a 606-base pair open reading frame encoding 202 amino acids including a classical signal peptide. This protein is produced locally by cells of the stromal compartment of tumors and is deposited into the extracellular matrix. Since tetranectin **binds** to **plasminogen** we hypothesize that it could function as an anchor and/or reservoir for **plasminogen** and similar substances that regulate tumor invasion and **metastasis** as well as tumor angiogenesis.

L32 ANSWER 42 OF 60 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 92058612 EMBASE
DOCUMENT NUMBER: 1992058612
TITLE: Retinoic acid-induced inhibition of **metastatic** melanoma cell **lung** colonization and adhesion to endothelium and subendothelial extracellular matrix.
AUTHOR: Edward M.; Gold J.A.; Mackie R.M.
CORPORATE SOURCE: University of Glasgow, Department of Dermatology, Anderson College Building, Glasgow G12 8QQ, United Kingdom
SOURCE: Clinical and Experimental Metastasis, (1992) 10/1 (61-67). ISSN: 0262-0898 CODEN: CEXMD2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The effect of pretreatment of **metastatic** B16 melanoma cells with 10-6 M all trans-retinoic acid resulted in a significant inhibition of **lung** colonization following injection of 105 cells into the tail

vein of syngeneic C57BL mice. Adhesion of melanoma cells to vascular endothelial cell monolayers, and subendothelial extracellular matrix was also inhibited by pretreatment with retinoic acid, as was tumour cell aggregation following seeding of pretreated cells on to 0.5% agar. Release of 35SO4 from radiolabelled subendothelial extracellular matrix by melanoma cells was essentially unaltered by retinoic acid pretreatment, as was the release of radiolabel from [3H]proline-labelled matrix, while **plasminogen** activator activity was enhanced in retinoic-acid-treated cells. These observed changes in adhesive properties may be responsible, at least in part, for the retinoic-acid-induced inhibition of **lung** colonization.

L32 ANSWER 43 OF 60 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 910513396 JICST-EPlus
TITLE: Successful thrombolytic treatment of spontaneous pulmonary embolism from caval tumor thrombus of renal cell carcinoma: A case report.
AUTHOR: KAWAI KOJI; YOKOYAMA MASAO; SHOJI FUMIO; FUJITO SHUSAKU; NISHIKAWA HIDEO
CORPORATE SOURCE: Toranomon Hospital
SOURCE: Hinyoki Geka (Japanese Journal of Urological Surgery), (1991) vol. 4, no. 5, pp. 513-516. Journal Code: L0465A (Fig. 4, Ref. 15)
ISSN: 0914-6180
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New

L32 ANSWER 44 OF 60 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 91331863 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1651300
TITLE: Differences in tetranectin immunoreactivity between benign and malignant breast tissue.
AUTHOR: Christensen L; Clemmensen I
CORPORATE SOURCE: Department of Pathology, Rigshospitalet, Copenhagen, Denmark.
SOURCE: Histochemistry, (1991) 95 (5) 427-33.
Journal code: 0411300. ISSN: 0301-5564.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911006
Last Updated on STN: 19911006
Entered Medline: 19910913

AB Tetranectin (TN) is a human, **plasminogen kringle** 4 **binding** plasma protein with ubiquitous cellular distribution and lectin-like characteristics. By means of the peroxidase-antiperoxidase staining technique a polyclonal and a monoclonal antibody were used to demonstrate TN within the intracellular as well as the extracellular compartment of invasive breast carcinoma. Whereas cell associated TN was universal showing only quantitative differences depending of the growth pattern of the tumor, 78 of 133 tumors displayed TN extracellularly as well. The occurrence of this stromal TN immunoreactivity was closely associated with desmoplasia, recognized morphologically by an increase in fibroblastic cells and immunohistochemically by an intense staining for the connective tissue glycoprotein fibronectin (FN). Benign breast tissue displayed a universal, intense cytoplasmic but no extracellular reaction

for TN, with the exception of rare foci of granulation tissue and around dilated cysts. Functional studies have shown that human embryonal **lung** fibroblasts increase their release of TN to the growth medium upon stimulation. The presence of TN extracellularly within fibroblast-rich foci of desmoplasia (and granulation tissue) suggests that a similar increased release of the protein takes place in vivo during active states. Desmoplasia has been found to have a protective effect on tumor cell propagation and **metastasis** in a murine model. The molecular interactions, which are responsible for this effect, are undoubtedly complex. However, TN may, by its specific **binding** to **kringle** 4 of **plasminogen** and its high affinity for sulphated polysaccharides, add to the understanding of how **plasminogen** activation is modulated at the local extracellular level.

L32 ANSWER 45 OF 60 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 91070514 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1701350
TITLE: Relationship between secreted urokinase **plasminogen** activator activity and **metastatic** potential in murine B16 cells transfected with human urokinase sense and antisense genes.
AUTHOR: Yu H R; Schultz R M
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, Loyola University Chicago, Strtch School of Medicine, Maywood, Illinois 60153.
CONTRACT NUMBER: CA 43305 (NCI)
SOURCE: Cancer research, (1990 Dec 1) 50 (23) 7623-33. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910308
Last Updated on STN: 20000303
Entered Medline: 19910122

AB Murine melanoma B16-F1 cells of low **metastatic** potential were transfected with the human gene for the prepro form of urokinase in an SV40 expression vector (plasmid pSV2-uPA), and cells expressing high amounts of the human urokinase gene product were selected for by an enzyme-linked immunosorbent assay specific for human high molecular weight urokinase. Southern analysis showed one of the cell lines (clone 7) had incorporated 150 copies of the pSV2-uPA plasmid into its genomic DNA. The human urokinase synthesized by the pSV2-uPA-transfected murine B16 cells was found to be **glycosylated** and did not **bind** to the murine cell surface urokinase receptor sites. In an in vivo assay that measures **metastasis** from a primary tumor (spontaneous **metastatic** assay), clone 7 cells showed an increased ability to **metastasize** (12 of 12 mice showed **metastatic** tumors), while control cells showed a lower ability to **metastasize** (only 2 of 11 mice showed **metastatic** tumors). In a second in vivo assay, which measures only the steps of the **metastatic** migration process during which tumor cells extravasate from the blood and then grow into pulmonary tumors (**lung** colonization assay), a significant multifold increase in the ability to form **lung** tumors was shown by the high human urokinase-secreting B16-F1 cells. In B16-F10 cells incorporating an antisense sequence to preprourokinase (plasmid pSV1-ASuPA-265) and secreting significantly decreased amounts of murine urokinase, a corresponding significant decrease in **lung**

colonization was observed. These results provide direct experimental support for a role of secreted (non-surface-**bound**) urokinase in the colonization steps of the **metastatic** process. Furthermore, the data indicate that the higher **lung** colonization ability of the B16-F10 line than of the B16-F1 line is primarily based on the quantitative differences in their abilities to produce urokinase.

L32 ANSWER 46 OF 60 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 88135650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2963689
TITLE: Modulation of **metastatic** potential by cell surface urokinase of murine melanoma cells.
AUTHOR: Hearing V J; Law L W; Corti A; Appella E; Blasi F
CORPORATE SOURCE: Laboratory of Cell Biology, National Cancer Institute, NIH, Bethesda, Maryland 20892.
SOURCE: Cancer research, (1988 Mar 1) 48 (5) 1270-8.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198803
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 20000303
Entered Medline: 19880328

AB We have carried out enzymatic, immunofluorescence, and surface iodination studies which show that B16 melanoma cells express the single chain form of the urokinase type **plasminogen** activator (uPA) on their cell surface, and that these cells are capable of **plasminogen** -dependent fibronectin degradation. The significance of the expression of surface single-chain uPA and uPA activity to the **metastatic** process was examined by **preincubating** melanoma cells with uPA modulating agents followed by i.v. injection of the cells into mice and enumeration of pulmonary nodules 17 days later. B16 cells that had been pretreated with anti-uPA immunoglobulins that were inhibitory to uPA activity invariably showed significantly decreased numbers of **metastases** compared to controls. On the contrary, pretreatment with plasmin, which is not only the product of the uPA catalyzed reaction but is also able to convert single-chain uPA to uPA, significantly increased the numbers of **metastases.** Control treatments, which included normal rabbit and mouse immunoglobulins, monovalent noninhibitory anti-uPA Fab fragments, and various monoclonal and polyclonal antibodies directed against other B16 cell surface antigens, did not affect the **metastatic** potential of the cells. Divalent inhibitory anti-uPA F(ab)2 fragments, on the contrary, inhibited **metastasis** as efficiently as intact IgG. The results support the hypothesis that proteolysis of extracellular matrix components by cell surface-localized uPA may be a critical step during the process of tumor cell invasion and **metastasis.**

L32 ANSWER 47 OF 60 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 86105933 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3943096
TITLE: Effect of butyric acid on **lung**-colonizing ability of cloned low-**metastatic** Lewis **lung** carcinoma cells.
AUTHOR: Takenaga K
SOURCE: Cancer research, (1986 Mar) 46 (3) 1244-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19990129
Entered Medline: 19860321

AB The **lung**-colonizing ability of low-**metastatic** Lewis **lung** carcinoma cells (P-29) was enhanced by their in vitro treatment with butyric acid and its sodium salt, sodium butyrate. Of the short chain fatty acids tested, butyric acid was the most effective in enhancing the **lung**-colonizing ability of P-29 cells; **propionic** acid and valeric acid were slightly effective, but acetic acid and caproic acid were ineffective. The enhancing effect of butyric acid on the **lung**-colonizing ability of P-29 cells was reversible, indicating that the result was the consequence of epigenetic alterations. Treatment of P-29 cells with butyric acid resulted in enhancement of secretion of **plasminogen** activator, cellular cathepsin B activity, and cellular adhesiveness. The phenotypes of cells treated with butyric acid were compared with those of cells treated with dimethyl sulfoxide, which was reported to enhance the **lung** -colonizing ability of P-29 cells. Significant differences were found in the phenotypes, especially that of cellular adhesiveness; that is, butyric acid enhanced mainly homotypic aggregation of the cells, while dimethyl sulfoxide enhanced mainly heterotypic adhesion, such as adhesion to monolayers of endothelial cells. In addition, butyric acid reversibly caused hyperacetylation of core histones in P-29 cells, while dimethyl sulfoxide did not.

L32 ANSWER 48 OF 60 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 86303107 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3744594
TITLE: Early spontaneous **metastasis** in the human epidermoid carcinoma HEp3/chick embryo model: contribution of incidental colonization.
AUTHOR: Gordon J R; Quigley J P
CONTRACT NUMBER: CA16740 (NCI)
SOURCE: International journal of cancer. Journal international du cancer, (1986 Sep 15) 38 (3) 437-44.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198610
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19861015

AB In the experimental model system where human tumor cells (HEp3) are implanted on the chorioallantoic membrane (CAM) of the chick embryo, **metastasis** of HEp3 cells to the embryonic **lung** occurs within a few days. Such rapidity in tumor dissemination makes this an attractive and potentially useful model for studying the **metastatic** process. The model, however, involves microvascular trauma at the site of implantation and thus tumor cells may accidentally enter the circulation during implantation or shortly thereafter. If these cells are the cause of the **lung metastasis** subsequently measured, the model would be in effect a colonization system and not a true, spontaneous **metastasis** system. The possible contribution of accidental **lung** colonization to secondary tumor

growth was therefore critically examined in this model. In standard **metastasis** assays, HEp3 was inoculated onto the CAMs of 10-day embryos, which were then **incubated** for various periods of time. The embryos' **lungs** were passaged to a second group of CAMs, **incubated** for 7 days to allow expansion of any HEp3 cells present, and then assayed for HEp3 cells by both microscopy and measurement of human **plasminogen** activator (PA) activity. **Metastasis** was evidenced by PA values above background (30 mU/mg protein). Morphological analysis of HEp3 cells in the embryonic **lung** correlated closely with PA values. To focus on the early stages of tumor dissemination when colonization might occur, the primary tumor was surgically excised from 38 embryos at various intervals after tumor inoculation, and after the operation embryos were allowed to develop to day 17. This procedure increased estimated assay sensitivity down to the level of 1 to 10 cells per **lung** in embryos operated on within 2 days of inoculation. Median PA values in the transplanted **lungs** were 13, 3, 37, 1,290 and 3,765 mU/mg protein in the groups operated on at 4 hr, 1, 2, 3 and 4 days after inoculation, respectively. Thus very few or no HEp3 cells arrest and grow in the **lungs** during the first 24 to 48 hr, but extensive **metastasis** occurs by 72-96 hr. Accidental colonization therefore plays no major part in the rapid pulmonary spread of HEp3 in this model.

L32 ANSWER 49 OF 60 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 85251404 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4040360
TITLE: Characterisation of rat tumour cell hybrids: procoagulant and fibrinolytic activities.
AUTHOR: Badenoch-Jones P; Ramshaw I A
SOURCE: Australian journal of experimental biology and medical science, (1985 Feb) 63 (Pt 1) 91-8.
Journal code: 0416662. ISSN: 0004-945X.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198508
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850809

AB The formation of **lung** colonies after i.v. injection of highly **metastatic** rat mammary adenocarcinoma cells (MAT 13762) was greatly reduced by concurrent treatment of rats with **heparin.** The procoagulant activity (PCA) of these cells, and of a non-**metastatic** adenocarcinoma (DMBA-8) has therefore been measured. These have been compared with PCA expressed by MAT 13762 cell derivatives including a non-**metastatic** hybrid clone (MAT 13762 X DMBA-8), its **metastatic** revertant, and clones selected in vivo from **lung metastases.** Potent PCA was expressed on intact MAT 13762 cells and in their spent culture media, the latter being sedimentable and associated with shed membrane vesicles. Cell-derived PCA, unlike thromboplastin, was equally effective in factor VII-deficient and normal bovine plasma. There were, however, no major differences in the expression of PCA (either cell-associated or shed) between the **metastatic** and non-**metastatic** cell types studied. **Plasminogen** activator (PA) production by these cells has also been measured. The results are discussed in the context of the possible role of fibrin formation and fibrinolysis in the **metastatic** process.

L32 ANSWER 50 OF 60 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on

STN
ACCESSION NUMBER: 1984:122448 BIOSIS
DOCUMENT NUMBER: PREV198427038940; BR27:38940
TITLE: TREATMENT WITH **TRANEXAMIC-ACID** DOES NOT MODIFY THE **METASTATIC** PATTERN OF A MURINE TUMOR.
AUTHOR(S): CONFORTI M G [Reprint author]; MUSSONI L; DONATI M B
CORPORATE SOURCE: LAB FOR HAEMOSTASIS AND THROMBOSIS RES, ITALY
SOURCE: Haemostasis, (1984) Vol. 14, No. 1, pp. 107.
Meeting Info.: 7TH INTERNATIONAL CONGRESS ON FIBRINOLYSIS, VENICE, ITALY, MAR. 27-30, 1984. HAEMOSTASIS.
CODEN: HMTSB7. ISSN: 0301-0147.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH

L32 ANSWER 51 OF 60 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 83022864 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6751364
TITLE: Ultrastructural study of the effects of **tranexamic acid** and urokinase on **metastasis** of Lewis **lung** carcinoma.
AUTHOR: Tanaka N; Ogawa H; Kinjo M; Kohga S; Tanaka K
SOURCE: British journal of cancer, (1982 Sep) 46 (3) 428-35.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198212
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 20000303
Entered Medline: 19821216

AB Lewis **lung** carcinoma cells were implanted in the foot-pads of mice and the effects of the **plasminogen**-plasmin inhibitor **tranexamic acid** (t-AMCHA) and of the **plasminogen** activator urokinase on **metastasis** were examined by electron microscopy. The intravascular tumour cells were not associated with thrombus formation in either control or urokinase-treated mice. Polymerized fibrin deposition around tumour cells and thrombi composed of fibrin and platelets was observed only in the mice given t-AMCHA. This suggests that the inhibition of fibrinolysis by tACC caused fibrin deposition and thrombus formation around intravascular tumour cells, which prevented release of the cells from primary foci to form secondary tumours. On the other hand, fibrinolysis induced by urokinase prevented thrombus formation, and accelerated cell release from primary foci.

L32 ANSWER 52 OF 60 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 24
ACCESSION NUMBER: 1983:200722 BIOSIS
DOCUMENT NUMBER: PREV198375050722; BA75:50722
TITLE: IN-VITRO DEGRADATION OF RADIO LABELED INTACT BASEMENT MEMBRANE MEDIATED BY CELLULAR **PLASMINOGEN** ACTIVATOR.
AUTHOR(S): SHEELA S [Reprint author]; BARRETT J C
CORPORATE SOURCE: ENVIRON CARCINOGENESIS GROUP, LAB PULMONARY FUNCTION TOXICOL, NATL INST ENVIRON HEALTH SCI, RES TRIANGLE PARK
SOURCE: Carcinogenesis (Oxford), (1982) Vol. 3, No. 4, pp. 363-370.
CODEN: CRNGDP. ISSN: 0143-3334.
DOCUMENT TYPE: Article
FILE SEGMENT: BA

LANGUAGE: ENGLISH

AB A simple and unique procedure for the **isolation** of intact basement membrane from Syrian hamster **lung** was developed. The method involved an initial 24 h extraction of minced **lungs** with 0.3 M acetic acid followed by treatment with N-lauroyl sarcosine, an **anionic** detergent. The tissue was washed several times in 0.85% NaCl and subjected to DNase treatment followed by washings with 0.85% NaCl and distilled water. The residue was shown to be basement membrane by EM and by amino acid analysis. The basement membrane was radiolabeled by reductive alkylation and had a specific activity of 3-5 + 105 glycoprotein component of the basement membrane. The abilities of malignant fibrosarcoma cell lines to degrade the [3H]basement membrane was examined. A simple assay to measure degradation of [3H]basement membrane was developed based on the solubilization of the insoluble material after degradation. When added to growing tumor cells in the presence of growth medium and serum, the [3H]basement membrane was solubilized extensively. The reaction was linear for 24 h at which time up to 90% of the labeled material had been released. In contrast, < 5% of the label was solubilized in medium plus serum alone or in the presence of normal Syrian hamster embryo cells. A preneoplastic cell line was also capable of degrading the [3H]basement membrane. The solubilization of the [3H]basement membrane was primarily due to degradation of the glycoproteins of the basement membrane as shown by Sephadex G-200 gel chromatography. The abilities of the tumor cells to degrade the [3H]basement membrane correlated with their fibrinolytic activity and inhibitors of plasmin inhibited the reaction. The activity of the cells in this assay was dependent upon the presence of **plasminogen** in the medium. No degradation of [3H]basement membrane was observed if **plasminogen** depleted serum was employed, but complete degradation was accomplished if purified **plasminogen** was added to the medium with **plasminogen**-depleted serum. These results indicate a role for **plasminogen** activator in the pathogenesis of invasive tumor cells.

L32 ANSWER 53 OF 60 EMBASE on STN

ACCESSION NUMBER: 82132565 EMBASE
DOCUMENT NUMBER: 1982132565
TITLE: Effects of **tranexamic acid** and urokinase on hematogenous **metastases** of Lewis **lung** carcinoma in mice.
AUTHOR: Tanaka N.; Ogawa H.; Tanaka K.
CORPORATE SOURCE: Res. Inst., Daiichi Seiyaku Co., Ltd., Edogawaku, Tokyo, Japan
SOURCE: Invasion and Metastasis, (1982) 1/3 (149-157).
CODEN: INVMDJ
COUNTRY: Switzerland
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
016 Cancer
015 Chest Diseases, Thoracic Surgery and Tuberculosis
LANGUAGE: English

AB When Lewis **lung** carcinoma with low thromboplastic and low fibrinolytic activities was implanted subcutaneously to mice, administration of **tranexamic acid** inhibited **metastasis** formation in the **lungs.** This effect was considered to be mediated by prevention of cell release from the implanted sites. Fibrin formation around tumor cells in the vessels of primary foci was observed in the mice given **tranexamic acid.** On the other hand, urokinase significantly enhanced pulmonary **metastases**

and many free tumor cells were observed intravascular in primary foci of the mice given urokinase.

L32 ANSWER 54 OF 60 MEDLINE on STN
ACCESSION NUMBER: 82096050 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7198597
TITLE: Effect of **tranexamic acid** on the growth and **metastasis** of V2 carcinoma in rabbits.
AUTHOR: Kodama Y; Tanaka K
SOURCE: Gann = Gan, (1981 Jun) 72 (3) 411-6.
Journal code: 8214471. ISSN: 0016-450X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198203
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19820322

AB The antifibrinolytic action of **tranexamic acid** (AMCHA) on the growth and **metastasis** of rabbit V2 carcinoma having high fibrinolytic activity was studied. Upon oral administration of AMCHA, the growth of the tumor and **metastasis** to the **lung** tended to be inhibited, and the number of **metastatic** foci in the regional lymph nodes significantly decreased in the early period of tumor growth. Enhancement of fibrin deposition in the tumor and inhibition of fibrinolytic activity of the tumor were recognized in the AMCHA-treated group. The inhibitory effect of **tranexamic acid** on fibrin dissolution might interfere with local tumor growth and the release of tumor cells into the vessels.

L32 ANSWER 55 OF 60 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 84238815 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7188385
TITLE: Effects of **tranexamic acid** and urokinase on hematogenous **metastases** of Lewis **lung** carcinoma in mice.
AUTHOR: Tanaka N; Ogawa H; Tanaka K; Kinjo M; Kohga S
SOURCE: Invasion & metastasis, (1981) 1 (3) 149-57.
Journal code: 8202435. ISSN: 0251-1789.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198408
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 20000303
Entered Medline: 19840821

AB When Lewis **lung** carcinoma with low thromboplastic and low fibrinolytic activities was implanted subcutaneously to mice, administration of **tranexamic acid** inhibited **metastasis** formation in the **lungs.** This effect was considered to be mediated by prevention of cell release from the implanted sites. Fibrin formation around tumor cells in the vessels of primary foci was observed in the mice given **tranexamic acid.** On the other hand, urokinase significantly enhanced pulmonary **metastases** and many free tumor cells were observed intravascularly in primary foci of the mice given urokinase.

L32 ANSWER 56 OF 60 MEDLINE on STN DUPLICATE 26

ACCESSION NUMBER: 81039443 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7191713
TITLE: **Plasminogen** activator in cultured Lewis **lung** carcinoma cells measured by chromogenic substrate assay.
AUTHOR: Whur P; Magudia M; Boston J; Lockwood J; Williams D C
SOURCE: British journal of cancer, (1980 Aug) 42 (2) 305-13. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198101
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810116

AB A chromogenic substrate assay for the **plasminogen** activator (PA) activity of Lewis **lung** carcinoma cells has been developed. The cells were **incubated** with **plasminogen**, the activation of which to plasmin was measured by the amidolysis of the chromogenic substrate S-2251. This was routinely performed as a 4h serum-free assay, but a variation lasting 24 h, in medium supplemented with **plasminogen**-free inhibitor-reduced serum, produced similar results. The assay also detected PA released into the medium. PA activity was proportional to cell density, and the assay was non-toxic to the cells. Assays were performed on cultures derived from primary and **metastatic** tumours. Host cells were effectively eliminated from such cultures but, because of an initial phase of tumour-cell death, PA assays were not carried out until cultures became established. No consistent difference was detected between PA levels in primary and **metastatic** cultures. However, these cultures were shown to be atypical of the parent tumour; they grew slowly when reinjected at the primary site, and their **metastatic** potential was impaired.

L32 ANSWER 57 OF 60 MEDLINE on STN
ACCESSION NUMBER: 67092940 MEDLINE
DOCUMENT NUMBER: PubMed ID: 5958850
TITLE: Effect of **heparin** and **plasminogen** inhibitor (EACA) on intravenously injected ascites tumour cells.
AUTHOR: Boeryd B
SOURCE: Acta pathologica et microbiologica Scandinavica, (1966) 68 (4) 547-52. Journal code: 7508471. ISSN: 0365-5555.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196704
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19670413

L32 ANSWER 58 OF 60 MEDLINE on STN
ACCESSION NUMBER: 67096299 MEDLINE
DOCUMENT NUMBER: PubMed ID: 5959842
TITLE: Effect of **heparin** and **plasminogen** inhibitor (EACA) in brief and prolonged treatment on intravenously injected tumour cells.
AUTHOR: Boeryd B

SOURCE: Acta pathologica et microbiologica Scandinavica, (1966) 68 (3) 347-54.
Journal code: 7508471. ISSN: 0365-5555.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196704
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19670421

L32 ANSWER 59 OF 60 MEDLINE on STN
ACCESSION NUMBER: 66150259 MEDLINE
DOCUMENT NUMBER: PubMed ID: 5884701
TITLE: Action of **heparin** and **plasminogen** inhibitor (EACA) on **metastatic** tumour spread in an isologous system.
AUTHOR: Boeryd B
SOURCE: Acta pathologica et microbiologica Scandinavica, (1965) 65 (3) 395-404.
Journal code: 7508471. ISSN: 0365-5555.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196609
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19660917

L32 ANSWER 60 OF 60 JAPIO (C) 2004 JPO on STN
ACCESSION NUMBER: 2000-106882 JAPIO
TITLE: ENZYME PRODUCING PLASMA PROTEIN HAVING TUMOR **METASTASIS** AND PROLIFERATION INHIBITORY ACTION AND PLASMA PROTEIN FRAGMENTED BY THE SAME
INVENTOR: **MORIKAWA WATARU**; KAMINAKA KAZUYOSHI; TAKEMOTO SUMIYO; MAEDA HIROAKI; NOZAKI CHIKAHIDE; MIYAMOTO SEIJI
PATENT ASSIGNEE(S): CHEMO SERO THERAPEUT RES INST
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2000106882	A	20000418	Heisei	C12N015-09

APPLICATION INFORMATION
STN FORMAT: JP 1998-296095 19981002
ORIGINAL: JP10296095 Heisei
PRIORITY APPLN. INFO.: JP 1998-296095 19981002
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2000
AN 2000-106882 JAPIO
AB PROBLEM TO BE SOLVED: To provide a novel nucleic acid fragment that comprises an enzyme producing fragments of plasma protein that has the inhibitory action of tumor **metastasis** and proliferation, hydrolyzes plasma protein, for example, **plasminogen**, fibronectin or the like and is useful for treatment of solid carcinomas. SOLUTION: This is an enzyme producing a novel protein fragment that produces a plasma protein fragment having a molecular weight of about 45

kDa according to a non-reduction system SDS electrophoresis, the amino acid residue at the N- terminus of LVRIPLHKFT, acts on plasma protein in an acidic region of a pH of <=5.0 to produce a fragment of a plasma protein having an inhibitory action of **metastasis** and proliferation of cancer and is an aspartic acid enzyme having a high homology to cathepsin D precursor or the like. Thus, this enzyme is useful for clinical treatment of solid cancers, for example, **lung** cancer, colon cancer and the like. This enzyme is obtained by maintaining human prostatic cancer cells (PC-3) in a medium including 10% fetal calf serum, substituting the culture medium with a serum-free medium, when they reach the confluent state, collecting the culture supernatant after culture, followed by centrifugation and filtration.